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Scientific Basis for Swedish Occupational Standards XXVI

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Preface

The Criteria Group of the Swedish National Institute for Working Life (NIWL) has the task of gathering and evaluating data which can be used as a scientific basis for the proposal of occupational exposure limits given by the Swedish Work Environment Authority (SWEA). In most cases a scientific basis is written on request from the SWEA. The Criteria Group shall not propose a numerical occupational exposure limit value but, as far as possible, give a dose-response/dose-effect relationship and the critical effect of occupational exposure.

In searching of the literature several databases are used, such as RTECS, Toxline, Medline, Cancerlit, Nioshtic and Riskline. Also information in existing criteria documents is used, e.g. documents from WHO, EU, US NIOSH, the Dutch Expert Committee for Occupational Standards (DECOS) and the Nordic Expert Group (NEG). In some cases criteria documents are produced within the Criteria Group, often in collaboration with DECOS or US NIOSH.

Evaluations are made of all relevant published original papers found in the searches. In some cases information from handbooks and reports from e.g. US NIOSH and US EPA is used. A draft consensus report is written by the secretariat or by a scientist appointed by the secretariat. The author of the draft is indicated under Contents. A qualified evaluation is made of the information in the references. In some cases the information can be omitted if some criteria are not fulfilled. In some cases such information is included in the report but with a comment why the data are not included in the evaluation. After discussion in the Criteria Group the drafts are approved and accepted as a consensus report from the group. They are sent to the SWEA.

This is the 26th volume that is published and it contains consensus reports approved by the Criteria Group during the period July 2004 through September 2005. These and previously published consensus reports are listed in the Appendix (p 73).

Johan Högberg
Chairman

Johan Montelius
Secretary

The Criteria Group has the following membership (as of September, 2005)

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Consensus Report for Hydrogen Fluoride, Aluminum Trifluoride, Ammonium Fluoride, Calcium Fluoride, Potassium Fluoride, Sodium Fluoride

September 15, 2004

This report is an update of the consensus report published in 1984 (146), which was based primarily on a criteria document from the Nordic Expert Group (72). It is based partly on an IPCS document (168). The EU published a risk assessment report for hydrogen fluoride in 2001 (41).

Chemical and physical data. Occurrence

Hydrogen fluoride

CAS No:	7664-39-3
Formula:	HF
Molecular weight:	20.01
Boiling point:	19.5 °C
Melting point:	- 83 °C
Vapor pressure:	90 kPa
Conversion factors:	1 mg/m^3 = 1.2 ppm
(20 °C, 101.3 kPa)	1 ppm = 0.8 mg/m^3

Sodium fluoride

CAS No:	7681-49-4
Formula:	NaF
Molecular weight:	41.99
Boiling point:	1704 °C
Melting point:	993 °C
Solubility in water:	42 g/l (20 °C)

Calcium fluoride

CAS No:	7789-75-5
Formula:	CaF_2
Molecular weight:	78.08
Boiling point:	2513 °C
Melting point:	1403 °C
Solubility in water:	0.016 g/l (20 °C)

Ammonium fluoride

CAS No:	12125-01-8
Formula:	NH_4F
Molecular weight:	37.04
Sublimation:	100 – 125 °C
Solubility in water:	820 g/l (20 °C)

Potassium fluoride

CAS No:	7789-23-3
Formula:	KF
Molecular weight:	58.10
Boiling point:	1505 °C
Melting point:	858 °C
Solubility in water:	920 g/l (20 °C)

Aluminum trifluoride

CAS No:	7784-18-1
Synonym:	aluminum-fluoride
Formula:	AlF_3
Molecular weight:	83.98
Sublimation point:	1291 °C
Solubility in water:	5 g/l (20 °C)

Fluorine (F) is a widely occurring element belonging to the halogen group, which also includes chlorine (Cl), bromine (Br), iodine (I) and astatine (At). The name is derived from early use of calcium fluoride as a flux (Latin *fluere*, *fluxus*: flow) (56). The salts of hydrofluoric acid are called fluorides. Fluorine is a pale yellow-green, irritating gas. It is extremely reactive and therefore seldom occurs in elemental form. Solutions of the water-soluble fluorides are usually acidic; only potassium fluoride has a weak alkaline reaction. Heating or contact with strong acids results in formation of hydrogen fluoride.

Anhydrous hydrogen fluoride is a colorless, sharp-smelling gas that occurs primarily as $(HF)_6$, although at higher temperatures it commonly occurs as the monomer (HF). Anhydrous hydrogen fluoride reacts strongly with sodium hydroxide, sulfuric acid and several organic compounds, and dissolves readily in water, forming hydrofluoric acid. Hydrogen fluoride is usually produced from fluorite by treating it with concentrated sulfuric acid. Anhydrous hydrogen fluoride in turn is used as a raw material in production of various organic and inorganic fluoride compounds: fluorocarbons, synthetic cryolite (Na_3AlF_6), aluminum trifluoride (AlF_3), gasoline alkylators etc., and also in the production of elemental fluorine. Hydrogen fluoride is also needed for synthesis of uranium tetrafluoride (UF_4) and uranium hexafluoride (UF_6), both of which are used in the atomic power industry. Hydrofluoric acid is used in oil refining, as a catalyst in

condensation reactions, as a preservative, for etching glass, semiconductors and metals, for tanning leather, and for removing rust and enamel from metal objects. Hydrogen fluoride can occur as an air pollutant in aluminum smelters and in brick, tile and ceramic production (18). Commercial hydrofluoric acid usually contains up to 53% hydrogen fluoride. It etches glass and dissolves quartz and silicates.

Sodium fluoride is a colorless or white powder, moderately soluble in water. Concentrated solutions are highly corrosive. Sodium fluoride is usually produced from hydrofluoric acid and sodium carbonate or sodium hydroxide (114). Sodium fluoride is used in steel and aluminum production (as a flux), acid baths, ceramic enamels, glass production, casein glue, detergents, paper coatings and insecticides; as a preservative; and for wood impregnation and fluoridation of drinking water (not in Sweden). Dilute solutions (0.02 – 0.2%) are used as mouthwash to strengthen tooth enamel (58, 114).

Calcium fluoride is a colorless solid, relatively insoluble in water as well as in dilute acids and bases (about 3000 times less soluble than NaF) (99, 114). It occurs in fluorite, a mineral that can be 60 – 97% calcium fluoride (168). Calcium fluoride is used in fluxes for production of steel and aluminum, in glass and enamel, and also in production of hydrogen fluoride and hydrofluoric acid (114). Calcium fluoride is also used in basic electrodes for welding (137, 138).

Ammonium fluoride occurs as white to colorless crystals resembling sand. It dissolves easily in water, forming a weak acid. It is used as a preservative and in wood impregnation, printing, coloring various materials, glass etching and moth repellents (158).

Potassium fluoride is a white, crystalline, caustic powder. It is soluble in water and weakly alkaline. On contact with strong acids it forms hydrogen fluoride. It is used to etch glass, as a preservative and insecticide, in production of elemental fluorine, and in fluxes for metal production (158).

Aluminum trifluoride, which is a Lewis acid, is a white, odorless but irritating solid that is only sparingly soluble in water (5 g/l). It is used in glass, porcelain and enamel; fluxes for welding and soldering; and in production of aluminum and aluminum silicate. The toxic effects of aluminum trifluoride are due not only to the fluoride, but to the aluminum also (93).

Uptake, biotransformation, excretion

Most occupational exposure is due to inhalation of dust and gas containing fluoride (63). Fluorides occur in industrial environments primarily in the form of dust, which with inhalation can penetrate the lungs – how deeply depends on particle size and solubility. The absorption of particulate fluorides increases with their solubility (84, 167). Autopsies of two cryolite workers showed an accumulation of fluorine in lung tissue due to inhalation of cryolite dust (10.8

and 79.2 mg F/100 g dry weight; unexposed control 0.73 mg F/100 g dry weight) (127).

Rats exposed by inhalation to 36 – 176 mg F^-/m^3 absorbed nearly all of it (110). The situation seems to be about the same for people (99).

Hydrogen fluoride has a permeability coefficient near that of water (P = 1.4 x 10^{-4} cm/s) measured in a lipid membrane consisting of lecithin and cholesterol (13). Skin and other tissues are rapidly permeated by diffusion of undissociated hydrogen fluoride, and effects on other organs can be the same as with inhalation. The rapid absorption seen after skin exposure to hydrogen fluoride may be partly a consequence of the corrosive nature of the substance, which damages blood vessels (168). After uptake, free fluoride ions bind to calcium and magnesium ions, forming insoluble salts (13, 157). There are no data from which to calculate quantitative skin uptake.

Soluble fluorides (e.g. sodium fluoride), once ingested, are absorbed rapidly and almost completely. Plasma fluoride concentration increases after only a few minutes, and a plasma peak proportional to the amount of intake usually can be measured within 30 minutes (36). Most fluoride is absorbed as hydrogen fluoride, which forms on contact with gastric acid (162). Hydrogen fluoride in aqueous solution diffuses through biological membranes mostly as the undissociated monomer HF (163). Absorption is by passive diffusion in both stomach and intestines. The absorbed amount can be considerably reduced by complex formation with e.g. calcium, magnesium or aluminum (161). In a bioavailability study, healthy volunteers were given 4 mg fluoride, as either calcium fluoride or sodium fluoride, in the form of tablets. They were monitored for 6 hours, with sampling after 0.5, 0.75, 1.0, 1.25, 2.0, 4.0 and 6.0 hours. After the sodium fluoride intake there was a rapid increase of plasma fluoride level and a peak after about 1 hour, but no increase in plasma fluoride level was seen in the subjects who had taken the calcium fluoride (3). Other sources, however, report a fluoride absorption of 67% for calcium fluoride (83).

The biological half time for fluoride in blood after oral intake of sodium fluoride is reported to be about 4 hours, although it seems to vary with the amount of intake (36). Fluoride is not metabolized, although it may form complexes with e.g. calcium or aluminum. It is distributed in blood to all organs in the body, and is reversibly bound to bone in the form of fluoride apatite. Bones and teeth contain 99% of all the fluoride in the body (53, 168). Volunteers were given ^{18}F by injection, and 1 hour later 40% of the dose was in extracellular fluid, 20% had been excreted, and 40% had been taken up in the tissues (including 2.5% in the red blood cells) (64). Fluoride also accumulates in hair and nails (25, 78, 165). The most important elimination pathway is via the kidneys, which excrete 40 – 60% of the daily fluoride intake (161); a further 5 – 10% of daily intake is eliminated in feces. Elimination in perspiration is apparently low (63), and only a minimal amount of fluoride makes its way into breast milk (38).

Biological exposure measurements

With both experimental and occupational exposure to fluoride, and for both oral and inhalation exposure, there is a relatively good correlation between exposure and fluoride levels in urine and blood (35, 39, 90, 161, 167).

Persons not occupationally exposed usually have fluoride levels in urine that are about the same as those in their drinking water (166). A survey of drinking water in Sweden, made during the 1960s, revealed that about 500,000 people drank water with a fluoride content above 0.8 mg/l (40 μmol/l) (140).

With occupational exposure to several types of fluoride compounds, there is a linear relationship between fluoride in air and in urine. The regression coefficients, however, differ with the compound in question. With exposure to hydrogen fluoride from hydrofluoric acid baths, urine fluoride level rose by 4.6 mg/l when fluoride in air rose by 1 mg/m^3 (63). For welding with basic electrodes containing calcium fluoride, urine fluoride level rose by 1.5 mg/l when fluoride in air rose by 1 mg/m^3 (137). In both of these studies, urine levels were measured after a workshift. The total amount of fluorides in urine of aluminum smelter workers (24-hour measure) rose by 3.9 mg/l when the fluoride in air increased by 1 mg/m^3 (32). It is reasonable to assume that these differences reflect differences in the solubility of different fluoride compounds.

In Germany there are biological exposure limits for urine content of fluorides as indicators of exposure to hydrogen fluoride and inorganic fluorides. The limit for fluorides is 7.0 mg/g creatinine after a workshift and 4.0 mg/g creatinine before a workshift (30).

The concentrations in saliva (37, 119, 164), hair and nails (25, 78, 165) have also been proposed as exposure measures, but there is limited information on the reliability of these methods (168).

It has also been proposed that fluoride in urine could be used as an exposure indicator for particles in smoke from welding with basic electrodes, since the smoke contains 18 – 20% fluorides (137).

Toxic effects

Effects on skin, eyes and respiratory passages

Hydrogen fluoride, hydrofluoric acid and acidic aqueous solutions of fluorides all have an irritating and corrosive effect on skin, eyes and mucous membranes. Machle *et al*. (94) exposed two volunteers to hydrogen fluoride. The highest concentration they could endure for more than one minute was 100 mg HF/m^3. Their skin began stinging within a minute, and they also reported irritated eyes and respiratory passages. A concentration of 50 mg HF/m^3 caused pronounced irritation of eyes and nose and stinging in the upper respiratory passages. A concentration of 26 mg HF/m^3 could be tolerated for several minutes, although slight stinging in nose and eyes was reported (94). One volunteer exposed to an average of 1.2 mg HF/m^3 (about 0.8 – 1.7 mg HF/m^3), 6 hours/day, 5 days/week for 15 days, endured the exposure with no notable effects on respiratory passages,

but the subject reported a slight burning sensation on the face (no skin reddening). Five volunteers were exposed to hydrogen fluoride in air concentrations averaging 2.1 – 3.9 mg/m^3, 6 hours/day, 5 days/week for up to 50 days; symptoms resulting from the exposure were burning sensations in skin, eyes and nose, and reddened and flaking skin resembling mild sunburn. No effects on lower respiratory passages were reported (83, 84). Exposing the eyes to higher concentrations results in redness, edema, photophobia and corneal necrosis (72).

Hydrogen fluoride and hydrofluoric acid are extremely caustic, and skin contact results in intense pain after a dose-dependent latency time. Damage to deep tissues and bone can occur with little effect on overlying skin. With hydrofluoric acid that is over 70% HF the effects appear immediately, whereas with concentrations below 50 – 60% it can take several hours for symptoms to appear (72). Skin uptake can result in severe and even fatal systemic poisoning (157). There are reports of non-lethal but severe poisonings resulting from industrial accidents. A 30-year-old man who was exposed to about 5 g anhydrous hydrogen fluoride on 2.5% of his skin had a blood fluoride value of <3 mg/l both 4 and 10 hours after the accident (12). Systemic poisoning in adults has also been reported after exposure of 2.5% of skin to 60% hydrofluoric acid (initial serum fluoride level 7.1 mg/l) and after exposure of 22% of skin to 70% hydrofluoric acid (initial serum fluoride level 6 mg/l) (55). In another case of severe systemic poisoning of an adult, about 5% of skin was exposed to anhydrous hydrogen fluoride (11).

There is a case report of a fatal poisoning of a 62-year-old man after skin contact with hydrofluoric acid (concentration unknown): 20% of his skin was damaged (55). Another fatal case was reported in which 2.5% of the skin was exposed to anhydrous hydrogen fluoride: serum fluoride level was reported to be 3 mg/l (150). A 23-year-old man died after 9 – 10% of his skin had been damaged by 70% hydrofluoric acid. His postmortem serum fluoride value was 4.17 mg/l (98). Two men, 50 and 60 years old, died after accidental exposure of face, chest, arms and legs to 70% hydrofluoric acid (15). A 37-year-old man died after about 8% of his skin was burned by about 150 ml 70% hydrofluoric acid (57). A 61-year-old man died after a 70% hydrofluoric acid solution was spilled on 8% of his skin. Four hours after the accident his serum fluoride value was 9.42 mg/l (111).

It has also been suspected that a particular type of skin change, Chiazzola maculae, which has been observed in persons living in an industrial area with fluoride emissions, might be caused by airborne fluorides. In a wide-ranging examination of the literature, however, Hodge and Smith (62) concluded that there is no support for this suspicion.

Tracheobronchitis, dyspnea, pulmonary edema and pulmonary hemorrhage, sometimes with fatal outcome, have been reported after inhalation of high hydrogen fluoride concentrations from accidental emissions (28, 115). Pulmonary edema has also been reported after absorption of hydrogen fluoride through the skin (150).

Single exposures to high doses of irritative substances can trigger an asthma-like disease – RADS (Reactive Airways Dysfunction Syndrome) – in persons with previously healthy respiratory systems (154). A 26-year-old, previously healthy

woman was exposed to HF while she was cleaning her toilet with a water-based rust remover containing 8 – 9% HF. After 1.5 to 2 minutes of scrubbing, her eyes, nose and mouth began to sting and she was having difficulty breathing. Her condition was initially regarded as RADS. It apparently developed into a chronic illness, since 2 years after the incident she was still being treated with broncho-dilators and cortisone, and had difficulty breathing with exertion and at night (43).

A new process for producing aluminum-fluoride was developed in a Swedish factory in the mid-1970s: fluosilic acid was heated with aluminum trihydrate in special ovens. During the development phase there were technical problems resulting in emissions from the ovens. It is reported that about 20% of the work-force of 35 – 40 persons suddenly developed problems with nocturnal wheezing and dyspnea. In the 1975-77 period there were 15 new cases of asthma, often after only a month or so of exposure, that were diagnosed during the following years at a lung clinic where diagnosis included methacholine tests. Dust measurements were taken around aluminum-fluoride production in the years 1975-77: stationary monitors showed air levels up to 53 mg/m^3 (n = 289, average 1975:15.8, 1976: 3.6, 1977: 1.0 mg/m^3) and personal monitors registered concentrations up to 13.5 mg/m^3 (n = 15, average 1975: 5.5, 1976: 2.6, no personal monitors used in 1977). About 25 – 30% of the dust had a particle size <5 μm. There was also a case report of a repairman who developed asthma the day after a heavy exposure. In two cases, provocation with aluminum-fluoride triggered no asthma symptoms. The authors attribute the appearance of asthma to the aluminum-fluoride exposure. It is clear, however, that the patients were simultaneously exposed to oven gases of unidentified composition, which might well be relevant. In 1977 the work environment was improved and the average exposure dropped to 0.4 – 1.0 mg/m^3, and in 1978 – 1982 there were 2 new cases of asthma (136).

Twenty healthy volunteers were exposed to various concentrations of HF in an exposure chamber for 60 minutes. Two of the subjects had hay fever and one of these had a high level of IgE (210 kU/l) (no information on which exposure group(s) contained these two subjects). The participants were divided into three exposure groups: 0.2 – 0.6 mg/m^3 (n = 9), 0.7 – 2.4 mg/m^3 (n = 7) and 2.5 – 5.2 mg/m^3 (n = 7). The subjects were exposed only once, except for three persons who were exposed twice with three months between exposures. The participants graded their symptoms on a special questionnaire before and after the exposure. Symptoms involving eyes and upper and lower respiratory passages were graded from 0 (“no symptoms”) to 5 (“most severe”). Upper respiratory symptoms increased with higher exposure. In the group with the lowest exposure, slight symptoms were reported by 4 of 9 ($p = 0.06$), in the middle group by 6 of 7 ($p = 0.10$) and in the group with highest exposure all 7 subjects reported symptoms (four ranked their symptoms 1 – 3, and three ranked their symptoms above 3) ($p = 0.02$). There was no clear dose-response relationship for symptoms involving eyes and lower respiratory passages. The reported severity of the symptoms was also included in the statistical processing. Nearly all the symptoms had disappeared four hours after the exposure. Lung function was measured before and after the

exposure, and no change in FEV_1 was observed. A slight but significant reduction of FVC was seen in the low-exposure group, but since it was not observed in the other groups it can not be interpreted as an effect of the exposure (90). There were few subjects in this study, and they were not given a null exposure to allow them to become accustomed to the exposure chamber. It is therefore difficult to assess the effect of the lowest exposure. The most probable LOAEL was estimated to be 0.7 – 2.4 mg/m^3.

When the same subjects (n = 19) were exposed to <0.6, 0.7 – 2.4 or 2.5 – 5.2 mg/m^3 hydrogen fluoride for one hour, the number of CD3-positive cells in the bronchial part of bronchial lavage fluid increased at the two higher exposures. Myeloperoxidase and inteleukin-6 increased at the highest exposure; this was regarded as an expression of an inflammatory reaction (91).

Seven of ten healthy volunteers who were exposed to 1 hour of hydrogen fluoride inhalation (3.3 – 3.9 mg HF/m^3) reported experiencing discomfort in nose and throat. Nasal lavages performed before and immediately after the exposure and 1.5 hours later revealed a significant increase in the numbers of neutrophilic granulocytes, total number of cells, tumor necrosis factor-alpha (TNF-α) and various eicosanoids, and an elevated concentration of antioxidants (92).

As early as 1936, occupational asthma was described in connection with electrolytic production of aluminum. This form of asthma was usually referred to as “potroom asthma” (45). Many studies of workers in aluminum smelters (electrolytic production) report effects on respiratory passages, including reduced lung capacity, irritation, asthma, coughs, bronchitis, dyspnea and emphysema. Among the substances these workers were exposed to were airborne fluorides (168). A correlation between fluoride exposure and the occurrence of asthma-like symptoms (dyspnea and wheezing) was observed many years later (77). In 26 persons with asthma-like symptoms there was a correlation between fluoride levels in plasma (as a measure of exposure) and bronchial response to metha-choline (142). Electrolytic production of aluminum is associated with exposure to a large number of airborne substances, including carbon monoxide, sulfur dioxide, hydrogen fluoride, polycyclic hydrocarbons and particles containing aluminum and fluorides (1), as well as small amounts of metals, including nickel, chromium and vanadium (141).

In a study of 370 potroom workers at an aluminum smelter it was found that complaints of bronchial symptoms and work-related asthma-like symptoms were more frequent among workers exposed to total fluoride levels >0.5 mg/m^3 than among workers exposed to <0.5 mg/m^3. Lung function studies were made, and no significant difference could be found. These workers were also exposed to sulfur dioxide. The prevalence of respiratory symptoms was independent of the level of dust exposure (141).

A historical cohort study of 5627 workers at two aluminum smelters in Norway contains an analysis of causes of death between 1962 and 1995. An association was found between emissions in the potrooms – which included fluorides

(calculated to have been between 0.1 – 1.7 mg/m^3), sulfur dioxide and aluminum oxide dust – and death due to chronic obstructive lung disease and asthma (128).

Chan-Yeung *et al*. (17), in a study of 797 workers (+713 workers in the office and casting departments with no significant exposure to air contaminants as controls) at an aluminum smelter, found that workers who spent >50% of their shift in the potrooms had higher frequencies of coughing and wheezing and significantly lower FEV_1 and maximum mid-expiratory flow values than the control group. The total fluoride level was reported to be 0.48 mg/m^3. These workers were also exposed to sulfur dioxide, aluminum oxide, carbon monoxide and benzo-[a]-pyrene (17).

Lung function and bronchial reactivity were measured in 38 potroom workers exposed to airborne fluorides and aluminum oxide. The workers were divided by job description into low-, medium- and high-exposure groups. Significant elevations in obstructive lung function changes and reduced diffusion capacity were seen when the potroom workers were compared to the control group. There was no observed difference between the high- and low-exposure groups. Methacholine tests revealed no increase in bronchial reactivity. The fluoride exposure was reported to be 0.31 mg/m^3 (85).

A study made in three aluminum smelters in Norway showed a low but significant correlation between fluoride in air and changes in lung function (FEV_1) during a workshift, and between fluoride concentrations in air and in urine. The air content was <2.5 mg/m^3, and the average post-shift urine concentration was <5.1 mg/l. Exposure measurements were also made for sulfur dioxide and carbon monoxide (71).

Elevated occurrences of respiratory problems and effects on lung function, sometimes with asthma, have thus been demonstrated in several studies of aluminum-fluoride production and in aluminum smelters (77, 136, 142). Since there was simultaneous exposure to several other substances including oven gases, the role of fluoride compounds in the reported health effects can not be determined with certainty. Although there were demonstrated correlations between fluoride in air and in urine, simultaneous exposure to other respiratory irritants may have caused or contributed to the health problems. No sensitizing mechanism has been described.

Direct application of sodium fluoride (0.5 or 1.0% in distilled water) to abraded skin of rats for 24 hours had effects ranging from superficial necrosis to edema and inflammation (40). Application of a 2% solution of sodium fluoride in water to the eyes of rabbits caused epithelial defects and conjunctival necrosis (54).

Effects on bones

High and prolonged uptake of fluoride leads to skeletal fluorosis, which is characterized by osteosclerosis (increased mineralization of the bones). This was first described in 1932 as an occupational disease of cryolite workers (109). Osteosclerosis itself is seldom a problem, but it can lead to brittle bones and a higher frequency of fractures, and a concurrent calcification of the tendons can

be painful and restrict movement (161). In a study of workers at an aluminum smelter, no osteosclerotic changes were found after 10 – 43 years of exposure to fluorides. Fluorine concentrations measured in urine were 2.78 mg/l before a workshift and 7.71 mg/l afterward (average values) (31). Chan-Yeung *et al*. (16) studied 2066 employees at an aluminum smelter in Canada. The subjects were divided into groups by fluoride exposure: 570 persons who spent at least 50% of their working time in the potroom were labeled "high-exposure" and 332 who spent less than 50% of working time in the potroom were labeled "medium-exposure". A group of 284 workers (e.g. welders) was labeled "mixed-exposure". There were also an unexposed internal control group consisting of 880 office workers and an external control group of 372 railroad workers. Airborne fluorides were measured with personal monitors. Fluoride concentrations measured in urine of the control group (total airborne fluorides 0.053 mg/m^3) were 1.2 mg/l before a workshift and 1.3 mg/l after a workshift (mean values); 1.9 mg/l (before) and 2.7 mg/l (after) in the high-exposure group (total airborne fluorides 0.48 mg/m^3); 1.4 mg/l (before) and 1.8 mg/l (after) in the medium-exposure group (total airborne fluorides 0.12 mg/m^3); and 1.5 mg/l (before) and 1.8 mg/l (after) in the mixed-exposure group (total airborne fluorides 0.46 mg/m^3). Levels of fluoride in urine were correlated to exposures. Hips were x-rayed in a subgroup of 136 workers in the high-exposure group, 41 in the medium-exposure group who had been employed in the potroom for more than 10 years, and 33 unexposed workers (internal controls). The x-rays showed slight indications of increased skeletal density in a few of those who had been exposed for more than 10 years. However, there was some disagreement among the radiologists as to how the x-rays should be interpreted . The authors concluded that there were no definite cases of skeletal fluorosis among the potroom workers at an aluminum smelter who were exposed to about 0.48 mg fluoride/m^3 for at least 50% of their time at work. There were no observed differences among the groups with regard to occurrence of back and joint problems. Blood tests showed no indications of renal, hepatic or hemato-poietic effects (16). In a review of older studies, it was concluded that the risk for occurrence of diagnosable osteosclerosis was high if the air concentration of fluoride at a workplace exceeded 2.5 mg/m^3 and/or fluoride in urine exceeded 9 mg/liter. However, workplaces where fluoride concentrations were below 2.5 mg/m^3 (and fluoride in urine below 5 mg/l) didn't seem to cause osteosclerosis (62). In a study in the phosphate industry, somewhat higher bone density was seen in 17 of 74 persons. Their average exposure was 2.81 mg F/m^3 and average length of employment was 14.1 years. No clinical symptoms were reported (29). In a Polish study of 2,258 workers at an aluminum smelter, skeletal changes were related (clinically and radiologically) to a qualitative 'exposure index' calculated from length of employment (average 17.6 years) and extent of levels exceeding the exposure limit (monitoring showed values up to 4 times higher than the Polish threshold limit of 0.5 mg HF/m^3) in various parts of the plant. The prevalence of skeletal changes was positively correlated to the 'index of exposure-years'. More pronounced changes were documented in older workers (26).

The connection between skeletal fluorosis and work-related intake of 0.2 – 0.35 mg F/kg body weight/day (via inhalation of cryolite dust) for several years was studied in cryolite workers in Copenhagen. Workers with mild osteosclerosis had been employed for an average of 9.3 years; pronounced cases had been employed for an average of 21.1 years (127). Osteosclerotic changes were documented in a person who had worked for 16 years with hydrogen fluoride production; 24-hour urine concentration was reported to be about 15 mg F/l (169). The relationship between hip fractures and fluoride in drinking water was examined in a retrospective cohort study in Finland. The study covered 144,627 persons who were born between 1900 and 1930 and who had lived in the same village without municipal water service for at least 13 years (1967 – 1980). The participants were divided into 6 groups according to the fluoride concentration in their drinking water. The total daily fluoride intake in the cohort was estimated to be 0.6 – 3.7 mg/day (including food and other fluoride sources such as toothpaste). The occurrence of hip fractures between 1981 and 1994 was established by checking hospital records. No association was found between fluoride concentration and occurrence of fractures, among either men or women, if all age groups were considered together. However, significantly elevated relative risk of hip fracture was seen in the highly exposed (3.7 mg F/day) women in the 50 – 65 age group when they were compared with the low-exposure (0.6 mg F/day) group (81).

The relationship between fluoride in drinking water and hip, vertebral and total fractures after age 20 was examined in a study of rural Chinese. The study covered 8,266 people from six regions with different fluoride concentrations in drinking water. The participants had lived in the same village for at least 25 years and were 50 years old or older. Drinking water and food were reported to be the only relevant sources of fluoride. Estimated daily fluoride intakes in the six regions were 0.73, 1.62, 3.37, 6.54, 7.85 and 14.13 mg. One or more fractures were reported by 531 persons: 526 of these were confirmed by x-rays, and 56 of these were hip fractures. A group with medium exposure (3.37 mg F/day) had the lowest number of fractures, and the differences between this group and the lowest (0.73 mg F/day) and highest (14.13 mg F/day) exposure groups were statistically significant. Analyses were also made of all fractures occurring after age 50: they showed the same tendency, but the difference was statistically significant only for the high-exposure group. The number of hip fractures was the same in the three lowest exposure groups, but then rose with rising fluoride exposure, and in the highest exposure group the increase was significant. For vertebral fractures there was no observed difference between the groups (89).

WHO has concluded that studies from India and China indicate some increase in risk of skeletal effects with intake (primarily via food and drink) of over 6 mg F/day. Significant effects were seen at intake of 14 mg F/day (168).

Skeletal changes seem to be slowly and at least partly reversible after fluoride exposure is stopped (53, 127).

Other toxic effects

Fluoride has high acute toxicity. The lowest potentially toxic oral dose is calculated to be 5 mg F/kg body weight (159). A definitely lethal dose for an adult weighing 70 kg is reported to be 5 – 10 g NaF (32 – 64 mg F/kg body weight) (61), but deaths among adults have been reported at much lower doses (<18 mg F/kg) (49). Among children, severe poisonings and several deaths have been reported in connection with non-therapeutic intake of tablets containing sodium fluoride, and in one case a 2-year-old child died after oral intake of about 4 mg F/kg (34). Deaths have also been reported after consumption of other products containing fluoride (wheel cleaner containing ammonium bifluoride) (75, 112).

Consumption of fluorides can have a range of acute effects: nausea, vomiting, stomach cramps, diarrhea, fatigue, drowsiness, coma, spasms, cardiac arrest and death (9, 73, 150). Cardiac arrest is believed to be due to development of hypocalcemia and/or hyperkalemia (9, 10, 24). Several cases of cardiac arrest and death have also been reported after skin contact with hydrogen fluoride (15, 55, 57, 98, 111). In one case, the patient died of heart failure due to necrotic cardiac muscles 12 days after drinking half a shot glass of 17.3% hydrofluoric acid (42).

In animal tests to determine LC_{50} values, rats, rabbits and guinea pigs have been exposed by inhalation to various concentrations of hydrogen fluoride. Rats were found to be most sensitive (LC_{50} 4142 mg/m^3 for 5 minutes, 1092 mg/m^3 for 60 minutes). Observed indications of toxicity were pronounced irritation of conjunctiva, mucous membranes and respiratory passages. The animals that survived the exposure recovered within a week. The animals that died had pathological changes in lungs, kidneys and liver, and necroses and inflammation in skin and mucous membranes (130). The LD_{50} for oral administration of sodium fluoride is reported to be between 36 and 96 mg F/kg body weight for rats and between 44 and 58 mg F/kg body weight for mice (160).

Fluoride apparently interferes with several enzyme systems, including cholinesterase and enzymes involved in glycolysis. This is regarded as a possible cause of the neuromuscular weakness and CNS depression seen with severe poisoning (9). Hypomagnesemia has also been observed following skin contact with hydrogen fluoride (15, 131).

Fluoride in low doses has a documented protective effect against caries, but chronic, high exposure leads to disruption in tooth mineralization (dental fluorosis), since fluoride interferes with enamel formation in the tooth buds. It shows up as white hypomineralized spots in the enamel, which in severe cases can be fairly large holes (73). The spots can grow darker with age.

No increase of hematopoietic, hepatic or renal dysfunction was seen in 570 aluminum smelter workers with an average 79 months of exposure to 0.48 mg fluoride/m^3 and an average after-shift urine value of 2.7 mg F/l (16). Nor was elevated occurrence of kidney disease seen in several epidemiological studies of people (both children and adults) with long-term exposure to drinking water with fluoride concentrations up to 8 mg F/l (47, 86, 125, 133). No indications of

significant negative hematological, hepatic or renal effects were found in a study of patients with osteoporosis. The patients (n = 163) had been taking about 60 mg sodium fluoride/day (equivalent to a dose of 389 μg fluoride/kg body weight/day for an adult weighing 70 kg) for 5 years (59). Yet another study examined post-menopausal women with osteoporosis (n = 25) who had been taking 23 mg fluoride/day (as sodium monofluorophosphate) for an average of 4.2 years (1.4 to 12.6 years). This equals a dose of 400 μg F/kg body weight/day for an adult weighing 58 kg. Average urine content was 9.7 mg F/l and average blood content 0.17 mg F/l. No clinically significant effects on studied parameters could be observed when blood and urine samples from the fluoride-exposed patients were compared with samples from a control group (68).

Reports of fluoride hypersensitivity are mostly of an anecdotal nature (108, 122, 125). Reported symptoms include dermatitis, urticaria, inflamed mucous membranes in the mouth, and gastrointestinal disturbances. Hypersensitivity to dental care products containing fluoride might be caused by either sodium fluoride or the color or taste additives (2).

High concentrations of fluoride *in vitro* (e.g. 10 mM NaF and 25 mM NaF) have been observed to disturb a number of cell processes through their effect on various enzymes and receptors (5, 107, 117, 120). The relevance of these observations *in vivo*, however, is unclear.

Genotoxicity

The ability of fluorides – especially sodium fluoride (NaF) – to damage genetic material has been tested in numerous systems, both *in vivo* and *in vitro*. There are also data from examination of exposed people.

Table 1 presents studies on the ability of fluorides to cause genetic mutations in bacterial tests (*Salmonella typhimurium*) and various mammalian cell lines *in vitro*. In Ames' tests with *Salmonella*, no mutagenic effect was observed even at high sodium fluoride concentrations, either with or without addition of metabolizing systems. However, mutagenic effects have been observed in some mammalian cell lines, especially at high concentrations of sodium fluoride.

Table 2 presents results from studies of the ability of fluorides to cause structural or numeric chromosome changes, primary DNA damage, gene conversion or meiosis disturbances in mammalian cells *in vitro* (Table 2a) and in laboratory animals *in vivo* (Table 2b). Sodium fluoride has been shown to damage genetic material in several cell lines (4, 116, 134, 155, 156). The picture is not that simple, however: there are also negative results, even at high doses (46, 151, 153). Nor are the results of *in vivo* tests entirely unequivocal. Most of the studies report no effects even after high exposures (40, 60, 70, 79), but there are also reports of effects at fairly low doses of sodium fluoride (121).

Table 1. Results of *in vitro* mutagenicity studies with bacteria (*Salmonella typhimurium*) and mammalian cells.

System	Fluoride dose	Effect tested	Result	Ref.
Salmonella	F 0.1-2000 μg/plate	histidine reversion	Negative	96
Salmonella	NaF 0.44-4421 μg/plate	histidine reversion	Negative	87
Salmonella	NaF 10-320 μg/plate	histidine reversion	Negative	153
Mouse lymphoma cells L5178Y	NaF 200-800 μg/ml 4 h	thymidine kinase	Positive at 300 μg/ml; 800 μg/ml caused cell death	14
Mouse lymphoma cells L5178Y	KF 300-700 μg/ml 4 h	thymidine kinase	Positive at 400 μg/ml; 700 μg/ml caused cell death	14
Human lymphoblastoid cells	NaF 100-600 μg/ml 28 h	thymidine kinase, hypoxanthine-guanine phosphoribosyl-transferase (HGPRT assay)	Effects only at concentrations resulting in significant cell death (12% survival)	23
Rat liver cells	NaF 2-40 μg/ml 72 h	HGPRT assay	Negative	153

There have been few studies of genotoxic effects on humans. In one study of fluoride-exposed workers in a phosphate fertilizer plant in China, it was found that the average frequency of sister chromatid exchanges (SCE) in lymphocytes in peripheral blood was about 50% higher in these workers (n = 40) than in an equally large group matched for age, sex and smoking habits (100). However, during the study period the workers were exposed not only to fluorine (mostly hydrofluoric acid and silicon tetrafluoride), 0.5 – 0.8 mg/m^3, but also to phosphate fog, ammonia and sulfur dioxide. Both ammonia and sulfur dioxide have been shown to give rise to chromosome aberrations (102, 103, 104, 171, 172). No information on the total amount of fluoride was presented. There was no correlation between duration of employment (<5, 5 – 10 or >10 years) and frequency of sister chromatid exchanges. In another study with the same exposure conditions (101), of workers (n = 40) at the same fertilizer plant, both chromosome aberrations and micronuclei in circulating blood lymphocytes were higher than in 40 controls matched for age, sex and smoking habits.

In the previously mentioned study (under *Other toxic effects*) of post-menopausal women with osteoporosis (n = 25) who had been taking 23 mg fluoride/day (as sodium monofluorophosphate) for an average of 4.2 years (1.4 – 12.6 years), sister chromatid exchanges in lymphocytes were no more frequent than in the control group (68).

Table 2a. Results of *in vitro* genotoxicity studies with mammalian cells.

System	Fluoride dose	Effect tested	Result	Ref.
Hamster embryo cells	NaF 50-200 μg/ml 16 and 28 h	Chromosome aberrations	Positive	155
Hamster embryo cells	NaF 20-80 μg/ml 24 h	Sister chromatid exchanges	Positive	155
Hamster ovarian cells	NaF 1.6-1600 μg/ml	Chromosome aberrations, sister chromatid exchanges	Positive	116
Hamster ovarian cells	NaF 2-40 μg/ml 24-72 h	Sister chromatid exchanges	Negative	153
Human lymphocytes	NaF 20-40 μg/ml 2-28 h	Chromosome aberrations	Positive	4
Human fibroblasts	NaF 20-50 μg/ml 12-24 h	Chromosome aberrations	Positive	156
Human fibroblasts	NaF 10-20 μg/ml 24-48 h	Chromosome aberrations	Positive	134
Human lymphocytes	NaF 4.2-42 μg/ml 2 h	Chromosome aberrations	Negative	46
Human lymphocytes	NaF 2-80 μg/ml 48 h	Sister chromatid exchanges	Negative	153
Human lymphocytes	NaF 4.2-420 μg/ml 48 h	Sister chromatid exchanges	Negative	151
Human lymphocytes	KF 5.8-580 μg/ml 48 h	Sister chromatid exchanges	Negative	151
Rat liver cells	NaF 160 μg/ml	Increased DNA repair activity	Negative	153

One study compares three groups (n = 66, 63, 70) of people who had lived for at least 30 years in areas with three different levels of fluoride in drinking water (0.1, 1.0 and 4.0 mg/l). The groups had different fluoride levels in urine (0.7, 1.1 and 2.8 mg/l) and blood (1.1, 1.8 and 4.0 μmol/l). A significant increase of sister chromatid exchanges was observed in those who lived in the high-exposure area. This group was studied further, and no difference in frequency of sister chromatid exchange was found between persons who drank fluoride-poor water from a spring and those who drank water with 4 mg fluoride/l. The authors concluded that the observed difference in sister chromatid exchanges was not related to the fluoride exposure (69).

Table 2b. Results of *in vivo* genotoxicity studies with mammalian cells.

Species/system	Fluoride dose	Effect tested	Result	Ref.
Mouse oocytes	NaF 16 x 250 μg s.c.	Meiotic abnormalities: anaphase lags, bridging, tetraploid nuclei etc.	Negative	70
Mouse oocytes	NaF 35 x 5 μg/g b.w. s.c.	Meiotic abnormalities: anaphase lags, bridging, tetraploid nuclei etc.	Negative	70
Mouse bone marrow cells	NaF 10-40 mg/kg i.p. or 40 mg/kg s.c. or 40 mg/kg p.o.	Chromosome aberrations	Positive	121
Mouse bone marrow cells	NaF 50 mg/l in drinking water for at least 7 generations	Sister chromatid exchanges, chromosome aberrations	Negative	79
Mouse bone marrow cells	NaF 7.5-30 mg/kg i.p.	Micronucleus test	Negative	60
Mouse bone marrow cells	NaF 2 x 10-40 mg/kg i.p.	Micronucleus test	Positive	121
Rat bone marrow cells	NaF 500-1000 mg/kg p.o.	Micronucleus test	Negative	4

s.c. = subcutaneous; i.p. = intraperitoneal; p.o. = per os

Another study examined the relation between fluoride content in drinking water (0.2, 1.0 and 4.8 mg/l) and the frequency of sister chromatid exchanges in lymphocytes. Persons in the low-exposure group had more sister chromatid exchanges than those in the two other groups (88).

In a survey article on the genotoxicity of fluoride, the question of whether fluoride gives rise to chromosome damage *in vivo* is judged to be still unanswered (175).

Carcinogenicity

Animal data

No significant increases in tumor occurrence were observed in early animal experiments on the carcinogenicity of fluorides (74, 148, 149), in which mice were exposed to sodium fluoride (NaF) in either drinking water or feed. The quality of these studies, however, was not sufficient to allow any definite conclusions, and the studies have been criticized for methodological shortcomings, including use of small, single-sex groups, poor age matching, single doses and brief observation periods (168). In one study (116), mice and rats were exposed to 0, 25, 100, or 175 mg NaF/liter in drinking water for 2 years: in two high-exposure groups of male rats there were more tumors than expected in bone tissue (1/50, 2/50). The number was not significantly higher than controls (0/50), but the dose-response trend was significant. No bone tumors were observed in

female rats or mice of either sex. The authors regard a connection to floride intake as doubtful. In another long-term study, rats were exposed to sodium fluoride in feed: three groups of 70 rats of each sex (+ control groups) were exposed to 4, 10 or 25 mg NaF/kg b.w./day for up to 99 weeks. No increase in cancer incidence was observed (97).

Human data

A number of epidemiological studies report elevated mortality due to various forms of cancer, especially lung and bladder cancer but also tumors in stomach, esophagus, pancreas, lymphatic-hematopoietic system, prostate and brain, in workers in the aluminum industry (6, 7, 50, 51, 106, 126, 129). Since these workers were also exposed to other substances (notably polyaromatic hydrocarbons) and no consistent pattern has been found, it would be unwarranted to connect the risk increase to fluoride exposure.

An elevated cancer morbidity has also been observed in the cryolite industry. A cohort study of cryolite workers (n = 522) in Denmark compared cancer mortality among these workers in the 1941-1989 period with mortality in the general population. There were elevated incidences of lung and larynx cancer (42 observed, 29.9 predicted) and bladder cancer (17 observed, 9.2 predicted). The workers had been exposed to cryolite dust (average dust levels 30 – 40 mg/m^3, estimated to be equivalent to a daily absorption of 14 – 70 mg fluoride by an adult weighing 70 kg.) and traces of quartz. The authors mention that a large portion of the cohort had probably been smokers. This might explain the elevation in lung and larynx cancer, but can only partially explain the elevated bladder cancer incidence. The results were interpreted as indicating that the elevated incidence of bladder cancer might be due to occupational exposure to fluorides (52).

In the United States, a population-based case-control study of fluorides and osteosarcoma cases (n = 130, illness diagnosed before age 24) in 1978 – 1988 found no correlation between the risk of developing the illness and non-occupational fluoride exposure (drinking water, mouthwash, toothpaste, fluoride tablets etc.) (48).

Several epidemiological studies in various parts of the world (including Australia, Canada, China and Taiwan, England and Wales, New Zealand, Norway and the United States) have examined the connection between cancer mortality and fluoride exposure via drinking water (33, 118, 139). In 1985, Knox (76) made an assessment of existing studies and concluded that no credible connections could be shown between cancer risk, elevated cancer mortality and water fluoridation or naturally occurring fluoride in water. A study by Yiamouyiannis and Burk (174) reported a correlation between drinking water fluoridation and cancer mortality. Their study was criticized for not adjusting for differences in age, race and sex in the compared groups, and the results have been questioned (76). Later studies have shown no connection between cancer and fluoride in drinking water (19, 44, 65, 95, 173).

The International Agency for Research on Cancer (IARC) has placed fluoride and sodium fluoride (66, 67) in Group 3: "the agent is not classifiable as to its carcinogenicity to humans".

Effects on reproduction

Animal data

Effects on testes and spermatogenesis have been seen in laboratory animals exposed to fluorides. In two studies, in which rabbits were given 10 mg NaF/kg b.w./day in diet for 18 or 29 months, structural changes in testes and sperm were observed after 18 months. In the group that was exposed for 29 months, spermatogenesis stopped (80, 145). Sprando *et al*. (143) reported that no effects on spermatogenesis – changes in sperm count, testes volume, histopathology – and no endocrine effects – serum testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) – could be seen in rats given drinking water containing 25, 100, 175, or 200 mg NaF/l for 14 weeks. A similar study with the same exposure levels gives the equivalent fluoride intakes: about 1.5, 5.6, 8.5 and 12.7 mg F/kg/day (21, 22). Nor were any effects on these parameters seen in the first generation of young (F_1 generation), exposed to these fluoride concentrations both *in utero* and after birth (143). In a follow-up study, no significant histological changes were seen in testes of F_1 rats exposed to these levels of sodium fluoride *in utero* and after birth (144).

In two studies of multigenerational effects and developmental toxicity of sodium fluoride, rats were given drinking water containing 0, 25, 100, 175 or 250 mg NaFl/l (free access) for three generations (F_0, F_1, F_2). The only effect observed was reduced calcification of the hyoid bone in the F_2 generation at the highest dose. No effects were seen in rats with lower intake, nor were any cumulative effects observed in the F_1 or F_2 generation (21, 22).

Rats were given drinking water containing 150 mg/l fluoride in the form of sodium fluoride (free access) before and during three gestations and during the subsequent lactation periods. Significant morphological changes were observed in femur shafts, under both light and scanning electron microscopes. However, no skeletal effects were observed in their pups (123, 124). No negative effects on fetal development were seen in pregnant rats given up to 25 mg NaF/kg b.w./day in drinking water on days 0 – 20 of gestation (20).

In a multigenerational study, female mice were given a low-fluoride diet and drinking water containing 0, 50, 100 or 200 mg fluoride/l. Reproduction was normal in the group given 50 mg/l, with regard to number of pups, occurrence of infertility, time to first litter and time between litters. At higher doses, however, growth inhibition, reduced reproduction and high mortality rates were observed. In the group given 200 mg/l, 50% of the mice died within 8 weeks and no young were produced (105).

Human data

Fluorides can pass through the placental barrier. Serum concentration in the mother has a direct relationship to that in the fetus (measured in umbilical blood): the level in umbilical blood is about 75% of that in the mother (135). In the fetuses fluoride is taken up in mineralized tissues (bones and teeth) (161). Data on fluorides and effects on human reproduction are sparse.

An elevated occurrence of spontaneous abortions (45% overrisk) was described in a nationwide study (14 companies) of female factory workers (n = 891) in the semiconductor industry. In addition to glycol ethers, fluoride compounds (hydrogen fluoride and ammonium fluoride) were identified as risk factors for occurrence of spontaneous abortions. The authors pointed out, however, that the observed correlation could be due to chance or to the existence of unidentified co-varying substances (132, 147). Personal monitors in 35 semiconductor manufacturing plants showed low exposure levels for fluorides, on average 0.001 mg/m^3 (<2% of the OSHA exposure limit of 2.5 mg/m^3) (170).

In two Russian studies, some effects on testosterone levels and luteinizing and follicle-stimulating hormones were seen among men who had worked in the cryolite industry for 10 to 25 years and who had diagnosed skeletal fluorosis (152). In another study, menstrual irregularities and irritation in the genital area were reported among women in the superphosphate industry (82), but since they had been exposed to several substances these effects could hardly be ascribed to fluoride alone.

A suspected connection between water fluoridation and increased prevalence of Down's syndrome (trisomy 21) was not confirmed in an American epidemiological study in which the prevalences of Down's syndrome between 1950 and 1966 in regions with and without water fluoridation were compared (113). Nor have case-control studies been able to show a correlation between fluoride and elevated risk of spontaneous abortions (8) or congenital heart disease (176).

Dose-effect / dose-response relationships

The effects of fluorides have been studied in both animals and humans. Table 3 (skin exposure), Table 4 (inhalation exposure) and Table 5 (oral exposure) present the studies in which relationships between symptoms and fluoride exposure have been examined in humans. Table 6 presents observations from animal experiments.

Skin uptake can lead to severe systemic poisoning, which has been reported after exposure to 60% hydrofluoric acid on 2.5% of the body surface (55). Fatal cases of poisoning have been described after burns from anhydrous hydrofluoride on 2.5% of the body surface (serum fluoride 3 mg/l) (150) and 70% hydrofluoric acid on 8% of the body surface (57, 111).

The lowest fluoride level judged to cause irritation in the upper respiratory passages is 0.7 – 2.4 mg HF/m^3 (90). At this exposure level there is also an

increase in the number of CD3-positive cells in the bronchial part of bronchial lavage fluid, and at 2.5 – 5.2 mg HF/m^3 there are indications of an inflammatory reaction (91). Indications of an inflammatory reaction were also seen in nasal lavage fluid at exposure to 3.3 – 3.9 mg/m^3 HF (1 hour), and 7 of 10 subjects reported upper airway discomfort (92). Slight burning sensations in nose and eyes were reported at exposure to 26 mg HF/m^3 for several minutes. At 50 mg HF/m^3, pronounced irritation of eyes and nose and stinging in the upper respiratory passages were reported after a few minutes of exposure. The highest concentration that two volunteers could endure for more than one minute, because of burning skin and irritated eyes and respiratory passages, was 100 mg HF/m^3 (94).

A slight stinging sensation in the face was reported by one person exposed to 1.2 mg HF/m^3 for 15 days. When 5 persons were exposed to 2.1 – 3.9 mg HF/m^3 for up to 50 days, they also developed slight irritation in eyes and nose and reddened, flaking skin resembling mild sunburn (83, 84).

Long-term exposure may lead to osteosclerosis. Prolonged exposure (over 10 years) to about 0.48 mg fluoride/m^3 for at least 50% of time at work yielded no confirmed cases of skeletal fluorosis. No indications of hepatic, renal or hematopoietic effects were seen (16). No cases of osteosclerosis were seen in aluminum smelter workers with 10 to 43 years of fluoride exposure and urine fluoride concentrations of 2.78 mg/l (pre-shift) and 7.71 mg/l (post-shift) (31). Somewhat elevated skeletal density was found in 17 of 74 persons with an average exposure of 2.81 mg F/m^3 and an average employment time of 14.1 years in the phosphate industry (29). Osteosclerosis appeared at a urine fluoride concentration of about 15 mg/l in conjunction with exposure to HF for 16 years (169). Skeletal fluorosis was associated with intake of 0.2 – 0.35 mg F/kg/day (inhalation of cryolite dust). Workers with mild osteosclerosis had been employed for an average 9.3 years, and those with pronounced osteosclerosis had been employed for an average 21.1 years (127).

A study in Finland examined the relation between hip fractures and fluoride content in drinking water. Total daily fluoride intake in the cohort was estimated to be 0.6 – 3.7 mg/day. A significantly elevated relative risk of hip fracture was seen in the highly exposed (3.7 mg F/day) women in the 50 – 65 age group when they were compared with the low-exposure (0.6 mg F/day) group (81).

The relation between fluoride concentration in drinking water and various fractures was studied in a population of Chinese villagers. A statistically elevated risk of fractures was identified in the high-exposure group (14 mgF/day) when these subjects were compared to groups with lower exposure (89).

No cases of osteosclerosis have been found in studies at workplaces with fluoride concentrations below 2.5 mg/m^3 (and urine fluoride below 5 mg/l). However, the prevalence of identifiable osteosclerosis was high if the air concentration exceeded 2.5 mg/m^3 and/or urine fluoride exceeded 9 mg/l (62). Although significant effects have not been demonstrated, WHO has concluded that there is some increase in risk of skeletal effects with an intake (mostly in food and drink) of over 6 mg F/day. Significant effects are seen at intake of 14 mg F/day (168). Using a dose of 6 mg/day as a basis, and assuming 100% uptake and

inhalation of 10 m^3 air per workday and 5 workdays/week, an air level of 0.8 mg F/m^3 would yield this daily dose. If this calculation is made for a dose of 14 mg F/day, the resulting air content would be 2.0 mg F/m^3.

Gastrointestinal side-effects have been reported with therapeutic intake of 30 mg NaF/day for 3 to 12 months (27). Therapeutic intake of 60 mg NaF/day (389 μg fluoride/kg/day for a person weighing 70 kg) for a period of 5 years resulted in no discernible hematological, hepatic or renal effects (59). Therapeutic intake of 23 mg fluoride/day for an average of 4.2 years had no effect on examined parameters in blood and urine samples, and yielded no increase in frequency of sister chromatid exchanges (68).

Elevated occurrences of sister chromatid exchanges, chromosome aberrations and micronuclei in blood lymphocytes were observed in conjunction with exposure to hydrofluoric acid and silicon tetrafluoride at levels of 0.5 to 0.8 mg/m^3. These workers were also exposed to phosphate fog, ammonia and sulfur dioxide (100, 101). On the other hand, in a study of fluoride content in drinking water (0.2, 1.0 or 4.8 mg/l) and frequency of sister chromatid exchanges in lymphocytes, a higher frequency was seen among persons in the low-exposure group (88).

No negative effects on fetal development were seen in rats given up to 25 mg fluoride/kg b.w./day in drinking water on days 0 to 20 of gestation (20). Structural changes in testes and sperm were observed in rabbits after intake of 10 mg NaF/kg b.w./day for 18 or 29 months, and in the group treated for 29 months spermatogenesis ceased (80, 145). Reduced ossification of the hyoid bone was observed in the third generation (F_2) of rats given drinking water containing 250 mg NaF/l; no effects were reported in groups with lower intake (21, 22). At this exposure there were no effects on spermatogenesis, no endocrine effects in F_0 or F_1 rats, and no testicular changes in F_1 rats (143, 144). Rats were given drinking water with 150 mg NaF/l for 10 weeks before and during 3 gestations and subsequent lactation periods, and morphological changes were found in femur shafts. There were no skeletal effects in their pups (123, 124). Reproduction in mice given drinking water containing 0, 50, 100 or 200 mg fluoride/l was normal in the 50-mg group. Higher doses caused growth inhibition, reduced reproduction and higher mortality rates. Half the mice in the group given 200 mg/l died within 8 weeks, and no young were produced (105).

In assessing the health effects of fluorides, background exposure must be considered. A substantial portion of the Swedish population ingests a fairly large amount of fluorides in food and drinking water.

Conclusions

The critical effect of long-term exposure to soluble fluorides is the effect on the bones. Calculations from WHO data, which is based on intake in food, indicate that skeletal effects appear at an air concentration of 0.8 to 2.0 mg F/m^3 for an 8-hour workday. In an epidemiological study, no definite indications of skeletal effects were seen with long-term exposure to 0.48 mg F/m^3. The critical effect

of acute exposure to airborne hydrogen fluoride, hydrofluoric acid and acidic aqueous solutions of fluorides is irritation of mucous membranes. This effect was reported at 0.7 – 2.4 mg/m^3 in a study with experimental exposure to HF. The toxicity of a fluoride is connected to its solubility: as a rule, less soluble fluorides are less toxic. Deaths have been reported after oral intake of extremely low doses – about 18 mg F/kg for adults, and even lower doses for children (about 4 mg F/kg).

As with other irritating substances, a single high exposure to HF can lead to acute (RADS) and permanent (asthma) damage to respiratory passages. Elevated occurrences of respiratory complaints and effects on lung function, sometimes with asthma, have been documented in several studies of aluminum-fluoride production and aluminum smelters. Since many other substances were also present, including oven gases, it is not possible to state with certainty the exact role of fluoride compounds in the appearance of these health problems.

Regarding cancer and genotoxicity, information is still not sufficient to allow assessment with acceptable certainty.

Fluoride passes through the placental barrier and can be taken up in mineralized tissue by the fetus, but toxic effects on reproduction have not been shown at doses relevant here.

Hydrogen fluoride is readily absorbed by the skin and can cause both local damage to deep tissues and systemic poisoning. Fatal cases have been reported.

Table 3. Effects of accidental skin exposure to hydrogen fluoride.

Exposure	Blood levels	Effects (subject)	Ref.
anhydrous HF, about 5 g 2.5% of skin	serum fluoride <3 mg/l 4 and 10 hours after the accident	Severe systemic poisoning (man, age 30)	12
anhydrous HF 2.5% of skin	serum fluoride 3 mg/l	Death (man)	150
70% hydrofluoric acid legs, about 9-10% of skin	serum fluoride postmortem 4.17 mg/l	Death (man, age 23)	98
70% hydrofluoric acid face, chest, arms and legs		Death (2 men, age 50 and 60)	15
70% hydrofluoric acid 8% of skin	serum fluoride 9.42 mg/l 4 hours after the accident	Death (man, age 61)	111
60% hydrofluoric acid 2.5% of skin	inital serum fluoride 7.1 mg/l	Severe systemic poisoning (man, age 38)	55
70% hydrofluoric acid 22% of skin	initial serum fluoride 6 mg/l	Severe systemic poisoning (man, age 50)	55
70% hydrofluoric acid, 150 ml legs, about 8% of skin		Death (man, age 37)	57
anhydrous HF arms, about 5% of skin		Severe systemic poisoning (man)	11

Table 4. Effects on humans exposed to fluorides by inhalation.

Exposure	Urine concentration	Subjects, Effects	Ref.
0.2-0.6 mg HF/m^3 1 hour		9 volunteers; 4 report slight upper respiratory symptoms (p=0.06). Slight reduction in FVC.	90
0.7-2.4 mg HF/m^3 1 hour		7 volunteers; 6 report slight upper respiratory symptoms (p=0.10). No change in FVC.	
2.5-5.2 mg HF/m^3 1 hour		7 volunteers; all 7 report upper respiratory symptoms (p=0.02) No change in FVC. (No clear dose-response relationship for symptoms involving eyes and lower respiratory passages, no change in FEV_1).	
0.2-0.6 mg HF/m^3 1 hour		No effect on bronchial lavage fluid.	91
0.7-2.4 mg HF/m^3 1 hour		Higher number of CD3-positive cells in bronchial lavage.	
2.5-5.2 mg HF/m^3 1 hour		Higher number of CD3-positive cells, myeloperoxidase and interleukin-6 in bronchial lavage (an expression of inflammatory reaction).	
3-6 mg AlF_3/m^3 (average) occupational		35-40 aluminum-fluoride production workers; 6 asthma cases in 1975, 7 in 1976.	136
0.4-1.0 mg AlF_3/m^3 (average) occupational		35-40 workers, same plant, improved conditions. 2 new cases of asthma 1978-1982.	
1.2 mg HF/m^3 (0.8-1.7 mg/m^3) 6 hrs/day, 5 days/wk, 15 days		1 volunteer; no noteworthy effects on respiratory passages, slight stinging of face. No skin reddening.	83, 84
2.1-3.9 mg HF/m^3 6 hrs/day, 5 days/wk up to 50 days		5 volunteers; slight stinging of face and eyes, slight nasal irritation; red, flaking skin resembling mild sunburn. No lower respiratory symptoms.	
3.3-3.9 mg HF/m^3 1 hour		10 volunteers; 7 reported upper respiratory irritation. Nasal lavage: significant increases of neutrophilic granulocytes, total number of cells, TNF-α, eicosanoids, antioxidant activity.	93
26 mg HF/m^3		2 men; endured for several minutes. Slight stinging of nose and eyes.	94
50 mg HF/m^3		2 men; after several minutes pronounced irritation of eyes and nose, stinging in upper airways.	
100 mg HF/m^3		2 men; highest concentration endurable longer than 1 minute. Stinging skin within 1 minute, irritation in eyes and airways.	

Table 4. Cont.

Exposure	Urine concentration	Subjects, Effects	Ref.
≈ 0.48 mg fluoride/m^3 ≥50% of workshift occupational	1.9 mg/l preshift, 2.7 mg/l postshift	Potroom workers in an aluminum smelter. No confirmed cases of skeletal fluorosis. Slight x-ray indications of higher bone density in a few workers with more than 10 years' exposure. No indications of renal, hepatic or hematopoietic effects.	16
<2.5 mg fluoride/m^3	<5 mg fluoride/l	In a review of older literature, no reported cases of osteosclerosis at workplaces with these levels.	62
>2.5 mg fluoride/m^3	>9 mg fluoride/l	Risk of osteosclerosis deemed high at workplaces with one or both these levels.	
2.81 mg F/m^3 occupational average 14.1 years		74 phosphate workers; 17 had somewhat elevated bone density.	29
hydrofluoride occupational 16 years	≈ 15 mg F/l	Osteosclerosis but no subjective symptoms.	169
occupational 10-43 years	2.78 mg F/l preshift 7.71 mg F/l postshift	Aluminum smelter workers; no osteosclerotic changes.	31
Cryolite dust (inhalation uptake of 0.2-0.35 mg F/kg b.w./day for several years)		Cryolite workers in Copenhagen; skeletal fluorisis. Mild osteosclerosis cases averaged 9.3 years exposure, pronounced cases averaged 21.1 years.	127
0.5-0.8 mg/m^3 hydrofluoric acid and silicon tetrafluoride occupational		40 workers in a phosphate fertilizer plant; average frequency of sister chromatid exchanges in circulating blood lymphocytes 50% higher than controls. (The workers were also exposed to phosphate fog, ammonia and sulfur dioxide.) No consistent correlation between length of employment and SCE. The same workers; a further study found increases in chromosome aberrations and micronuclei in lymphocytes.	100, 101

Table 5. Effects on humans of oral intake of fluorides.

Intake	Urine/blood concentration	Effects	Ref.
		In studies from India and China:	168
>6 mg F/day		Indications of higher risk of skeletal effects.	
>14 mg F/day		Clear increase in risk of skeletal effects.	
fluoride in water <0.1–2.4 mg/l; daily fluoride intake 0.6–3.7 mg		Finnish study on hip fractures and fluoride in drinking water: 6 exposure groups. Relative risk of hip fracture was higher for women at 3.7 mg/day (highest) than at 0.6 mg/day (lowest).	81
daily fluoride intake 0.73–14.13 mg		Study on bone fractures and fluoride in drinking water of Chinese villagers: 6 exposure groups. High-exposure group (14 mg F/day) had significantly more fractures than a medium exposure group and more hip fractures than a low-exposure group.	89
about 4 mg F/kg b.w.		A child (age 2) died after eating fluoride tablets.	34
5 mg F/kg b.w.		Calculated to be the smallest potentially toxic dose.	159
5–10 g NaF/kg b.w. (32–64 mg F/kg b.w.)		Lethal dose for an adult weighing 70 kg (LD_{100}).	61
about 18 mg F/kg b.w.	55 mg F/l in urine	An accidental death (adult) in Alaska due to high fluoride content in drinking water (150 mg F/l).	49
30 mg NaF/day 3-12 months		Treatment for osteosclerosis. Side-effects: stomach pains, nausea, vomiting, damage to gastroduodenal mucous membranes.	49
23 mg fluoride/day 1.4 to 12.6 years	9.7 mg F/l in urine (avg.) 0.17 mg F/l in blood (avg.)	Average intake for 4.2 years (average). No clinically significant effects on studied parameters in blood or urine samples compared to controls. No increase in SCE.	68
60 mg NaF/day about 5 years		Osteoporosis patients. No indication of significant negative hematological, hepatic or renal effects.	59
fluoride in drinking water	fluoride in urine mg/l / blood µmol/l	Comparative study of 3 groups living at least 30 years in areas with different fluoride levels in local water.	69
0.1 mg/l	0.7 / 1.1	n=66	
1.0 mg/l	1.1 / 1.8	n=63	
4.0 mg/l	2.8 / 4.0	n=70, Significant increase in SCE. This group was studied further, and there was no difference in SCE between those who drank water from a fluoride-poor spring and those who drank water with 4 mg fluoride/l. It was concluded that the difference in SCE was not caused by fluoride exposure.	
fluoride in drinking water		Study of fluoride in water supply and frequency of SCE in lymphocytes.	88
0.2 mg/l		Elevated frequency of SCE in lymphocytes.	
1.0 mg/l		No elevation in SCE.	
4.8 mg/l		No elevation in SCE.	

Table 6. Effects on laboratory animals experimentally exposed to fluorides.

Exposure	Species	Effects	Ref
In feed, NaF, 10 mg/kg/day	Rabbit		80,
18 months		Structural changes in testes, sperm	145
29 months		Spermatogenesis stopped	
In drinking water, NaF	Rat	No effects on spermatogenesis, no	143,
14 weeks		endocrine effects (serum testosterone,	144
25 mg/l (1.5 mg F/kg b.w.)		LH, FSH) in F_0 and F_1	
100 mg/l (5.6 mg F/kg b.w.)			
175 mg/l (8.5 mg F/kg b.w.)			
200 mg/l (12.7 mg F/kg b.w.)			
In drinking water, NaF	Rat		21,
F_0, F_1, F_2 generations			22
0 mg/l		No effect	
25 mg/l		No effect	
100 mg/l		No effect	
175 mg/l		No effect	
250 mg/l		Reduced ossification of hyoid bone, F_2	
In drinking water	Rat	No visible effects on fetal development	20
≤2.5 mg fluoride/kg b.w./day			
days 0-20 of gestation			
In drinking water	Mouse	Multigeneration study:	105
0 mg/l		Normal reproduction	
50 mg/l		Normal reproduction	
100 mg/l		Growth inhibition, reduced reproduction, high mortality	
200 mg/l		50% of mice died within 8 weeks	
In drinking water, NaF	Rat	Morphological changes in femur shafts	123,
150 mg/l		No effects on young	124
10 weeks before, during			
3 gestations, following lactations			
NaF, p.o.	Rat	LD_{50}	160
36 – 98 mg F/kg b.w.			
NaF, p.o.	Mouse	LD_{50}	160
44 – 58 mg F/kg b.w.			
HF, inhalation, 5 minutes	Rat	LC_{50}	130
4142 mg/m^3			
HF, inhalation, 15 minutes	Rat	LC_{50}	130
2242 mg/m^3			
HF, inhalation, 30 minutes	Rat	LC_{50}	130
1700 mg/m^3			
HF, inhalation, 60 minutes	Rat	LC_{50}	130
1092 mg/m^3			
HF, inhalation, 15 minutes	Guinea	LC_{50}	130
3608 mg/m^3	pig		

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Consensus Report for Inorganic Lead

December 8, 2004

This Report is based primarily on a criteria document compiled at the request of the Swedish criteria group (19) and updates a previous Consensus Report published in 1992 (10).

Chemical and physical data

Lead is a very soft metal and occurs naturally as four isotopes: 204, 206, 207 and 208. In damp air the metal rapidly develops an oxide coating that protects it against further oxidation. Above the melting point, however, oxidation continues, and first lead(II) oxide and subsequently lead(II, IV) oxide are formed. Lead in inorganic compounds usually has the oxidation number +II, but +IV can also occur. Lead(IV) compounds are readily reduced to lead(II) compounds.

Lead in combination with acids can yield lead(II) salts. Although these salts have notable ion-binding capacity, most lead(II) salts are only sparingly soluble. The most important readily soluble lead(II) salts are lead(II) nitrate and lead(II) acetate (7, 18).

Table 1. Some chemical and physical data for lead and some inorganic lead compounds.

Name	Formula	CAS No.	Mol. weight	Melting point (°C)	Boiling point (°C)	Solubility in water (g/liter)
Lead [1]	Pb	7439-92-1	207.2	327.5	1740	insoluble
Lead(II) acetate	$Pb(C_2H_3O_2)_2$	301-04-2	325.3	280	–	443
Lead(II) nitrate	$Pb(NO_3)_2$	10099-74-8	331.2	290*, 470*	–	377
Lead(II) chloride	$PbCl_2$	7758-95-4	278.1	501	950	9.9
Lead(II) sulfate	$PbSO_4$	7446-14-2	303.3	1000, 1170	–	0.042
Lead(II) carbonate, basic	$2PbCO_3 \cdot Pb(OH)_2$	1319-46-6	775.6	400*	–	insoluble
Lead(II) phosphate	$Pb_3(PO_4)_2$	7446-27-7	811.5	1014	–	insoluble
Lead(II) chromate(VI)	$PbCrO_4$	7758-97-6	323.2	844	–	insoluble
Lead(II) sulfide	PbS	1314-87-0	239.3	1114	1281	insoluble
Lead(II) oxide	PbO	1317-36-8	223.2	888	1470	insoluble
Lead(II,IV) oxide	Pb_3O_4	1314-41-6	685.6	500*	–	insoluble
Lead(IV) dioxide	PbO_2	1309-60-0	239.2	290*	–	insoluble

* disintegrates

[1] Conversion factors: 1 μg = 0.00483 μmol; 1 μmol = 207 μg

Occurrence, use

In Sweden, exposure to environmental lead comes mostly from lead in food, with lesser contributions from such sources as ambient air, water and tobacco. Lead exposure also occurs in some work environments, notably lead smelters, brass and bronze foundries, glassworks, battery manufacture and manufacture of PVC products. Lead exposure also occurs in the construction business, around demolition of plate coated with red lead, and sanding and renovation jobs involving materials coated with lead-based paint (18, 19, and personal communication from the Swedish Confederation of Trade Unions [LO]).

Uptake, biotransformation, excretion

Lead can be taken up by the lungs and digestive tract. Soluble lead compounds can also be taken up by skin to some extent, but no quantification of skin uptake can be made from existing data. Occupational exposure occurs primarily via inhalation, although some lead at workplaces can be taken up orally. Large particles are deposited high up in the respiratory passages, swallowed and to some extent absorbed from the digestive tract. Average uptake from the digestive tract of an adult has been reported to be about 15 to 20%. Roughly 40% of small particles (particle size ≤1 μm; e.g. lead smoke) are deposited in alveoli and absorbed there. The fraction is lower for larger particles. The absorption rate, and thus uptake, depends on the solubility of the lead compound in question (10, 18, 19).

After uptake, lead is found in blood – nearly all of it in the red blood cells. About 80% of the lead in red blood cells is bound to the enzyme δ-aminolevulinic acid dehydratase (ALAD). ALAD has three distinct isoenzyme phenotypes: ALAD 1-1 ($ALAD^1$), ALAD 1-2 and ALAD 2-2 (both called $ALAD^2$). About 80% of the Swedish population has ALAD 1-1, 19% ALAD 1-2 and 1% ALAD 2-2. $ALAD^2$ has a higher binding capacity for lead than $ALAD^1$. Lead in serum/plasma accounts for only a few percent of the total amount of lead in blood, but is probably the most biologically available portion of blood lead. The average content of lead in the blood of men not occupationally exposed has been gradually declining in Sweden, and in 1999 was about 0.2 μmol/l (10th percentile about 0.1, 90th percentile about 0.4 μmol/l) (21). Concentrations in women are about 25% lower (21). The soft tissues with the highest lead concentrations are liver and kidneys. The half time for lead in blood and soft tissues is about 3 to 4 weeks, but contributions from bone, where lead has a half time of years or decades, cause the blood lead in persons with long-term exposures to drop much more slowly when exposure decreases. Some lead passes through the blood-brain barrier. The peripheral nervous system also accumulates lead. Lead is distributed to the reproductive organs as well, and passes the placental barrier. Lead content in blood of newborn babies is correlated to that in their mothers, but is somewhat

lower. Lead is also excreted in breast milk, and nursing can be a major source of exposure to a baby even though the concentration in breast milk is much lower than that in the mother's blood (18, 19).

A large proportion of absorbed lead is incorporated into bone, which contains about 95% of the lead in the body. The accumulation pattern for skeletal lead varies, however: persons with the *ALAD*^{2} genotypes seem to accumulate less than persons with the *ALAD*^{1} genotype. The average amount of lead in the bones of lead workers has been reported to be about 100 mg, and the amount in Scandinavians without occupational exposure is reported to be about 8 – 10 mg. Lead in bone constitutes a good measure of long-term exposure. Lead is liberated from the bones, and this "endogenous" exposure can account for a considerable amount of the lead in blood. Liberation of skeletal lead can continue for decades after occupational exposure has stopped. The liberation rates for different types of bone vary considerably. Liberation of lead from bone increases during periods of high bone demineralization, such as during pregnancy or lactation, or after menopause. Liberation is higher during lactation than during pregnancy. There is large individual variation in the kinetics of lead metabolism in both soft tissues and bone (18, 19).

Lead is eliminated from the body primarily in urine and feces. Urinary excretion occurs by filtration in the glomeruli, probably followed by partial resorption in the renal tubules. There is large individual variation in urinary lead excretion at a given blood lead value (18).

Biological exposure measures

Biological monitoring of lead exposure has numerous advantages: it compensates for variations in respiration and in the particle size and solubility of lead compounds, it includes different exposure pathways (differences in hygiene), and it also reflects non-occupational exposure. Blood lead – especially considering the abundant documentation – is regarded as the most useful measure for assessing dose-effect relationships. A single blood lead value, however, is not a good measure of earlier exposure. Cumulative blood lead or bone lead can be a better measure of long-term exposure. Measurement of bone lead by X-ray fluorescence has been quite widely used in recent years, but experience is still limited. There can also be some degree of uncertainty in the analyses, particularly at low blood lead levels. Among other limitations with using blood lead as an exposure measure is that there is a curvilinear correlation between blood lead levels and uptake. At air lead concentrations lower than about 50 $\mu g/m^3$, a small increase in exposure can yield a large increase in blood lead and the correlation between blood lead and air lead is virtually linear. At higher air lead concentrations blood becomes saturated (especially the binding to ALAD) and the curve gradually flattens out: i.e. the increase in blood lead is proportionally less. Plasma lead probably has a linear relationship to uptake and effects, but experience here is still limited (18, 19).

There can be considerable variation in blood lead levels at the same concentration of lead in air, due to individual factors (differences in previous lead exposure, background exposure, lead metabolism, hygiene) and to differences in particle size and solubility of lead compounds. Consequently, it is difficult to translate a blood lead value to an air lead value, especially at the individual level. Attempts have been made to correlate total lead uptake in the body (from food, drink, air etc.) to blood lead levels in adults, using data from population studies and experiments with volunteers. They have a wide range of possible interpretations (18). An estimate based on this material indicates that persons with low background exposure can reach an average blood lead level of about 1.5 μmol/l at an air concentration of about 30 $\mu g/m^3$, with inhalation of lead compounds having small particle size (≤1 μm) and high solubility (18). Several more recent studies, including some of battery production workers, yield about the same correlation. Some of these studies also indicate that an air lead level of about 10 $\mu g/m^3$ should correspond to a blood lead level of around 1 μmol/l (8, 12, 19). Other data show that improving work routines (personal hygiene) can be an effective way to reduce blood lead levels (11).

Battery workers can be exposed to inorganic lead in the form of dust or smoke, and the lead can occur in metallic or oxide form or as lead sulfate (11, 15, 19). Exposure to less soluble lead compounds, which are biologically less accessible, results in blood lead levels that are generally lower than they are in the battery workers. In one study, a group average blood lead level of barely 1.5 μmol/l was found in workers exposed to lead silicate in the production of lead crystal, even when lead in air was around 200 $\mu g/m^3$ (15).

Toxic effects

There is a wide variation in effects among people with the same blood lead values. Some persons can develop lead poisoning at low blood lead levels, while others with much higher levels show little or no effect (18). Factors that affect sensitivity to lead include its distribution in the body and the bioavailability of lead bound in different tissues. Genetic polymorphism for *ALAD* could also explain some of the individual differences in sensitivity to lead (19).

The nervous system

Severe poisoning with symptoms involving the central nervous system (encephalopathy) has been reported at blood lead levels around 4 μmol/l (Table 2). Individuals with no definite clinical symptoms of encephalopathy can have subjective, non-specific symptoms (fatigue, anxiety, irritability, concentration and memory problems, sleep disturbance), as well as poorer performances on psychometric tests (18). Effects on the central nervous system (CNS) have been indicated in various neuropsychological tests (tests that measure concentration, coordination and memory as well as more complex functions) given to groups of

workers with average blood lead values of 1.5 – 2 μmol/l, but only in some of the tests used in each study. There are also limited data suggesting that slight CNS symptoms can occur at about this blood lead value (group average) (19). There is some uncertainty in interpreting these data, due in large part to the difficulty of estimating exposures and the choice of control groups. Slight CNS effects have been reported in children (exposed prenatally, via mother's milk and during their first years of life) at an average blood lead level of <0.5 μmol/l (see below under Reproduction).

Exposure to lead can also damage the peripheral nervous system (PNS) and in rare cases cause peripheral neuropathy with paralysis. Clinical symptoms and indications of effects on the motor and/or sensory PNS are apparently common at blood lead values around 3 to 3.5 μmol/l or higher (18), but slight sensory symptoms and indications of reduced muscular strength have been reported in exposed workers with group average blood lead values around 1.5 μmol/l. Disturbances of nerve conduction velocities in motor and sensory nerves and effects on perception of vibrations have been observed at an average blood lead level of about 1.5 μmol/l. Effects on the autonomic nervous system (primarily reduced heart rate variability) have also been reported in groups with average blood lead levels around 1.5 μmol/l (18, 19).

Subclinical (negative) effects on balance have been reported to occur at group average blood lead levels of about 1.5 μmol/l and higher. Effects on some complex functions (including visual and auditory evoked potentials, EEG) and, in one study, subclinical effects on vision (poorer contrast perception) have also been reported in groups with average blood lead levels of about 1.5 μmol/l and higher (19). In children, slight effects on hearing have been noted at group average blood lead values of about 0.5 μmol/l – even lower in one study (19).

It is not clear whether current exposure or long-term exposure (months/years) has more relevance to effects on the nervous system. Some data indicate that at least some effects (e.g. encephalopathy, peripheral neuropathy) can be completely or partly reversible if exposure is reduced (19).

Blood and blood-forming organs

High exposure to lead can cause anemia by inhibiting certain enzymes and thus disrupting heme and nucleic acid metabolism as well as hemolysis. Inhibition of the enzyme ALAD leads to metabolic blockage, with increase of δ-aminolevulinic acid (ALA) in plasma and urine. The metabolic interaction with lead also results in accumulation of coproporphyrin in plasma and urine, and of protoporphyrins in red blood cells (18). Lead in plasma is considered to be more closely correlated to ALA in plasma and urine and to coproporphyrin in urine than is lead in blood. Disturbance of heme metabolism is more pronounced in women than in men. Some data also suggest greater effects on heme metabolism in persons with the $ALAD^1$ genotype than in persons with the $ALAD^2$ genotypes. Effects on heme synthesis can affect the organism in ways other than causing anemia. Heme is

a component of enzymes involved in energy metabolism in all cells. The body's ability to detoxify foreign substances can also be reduced. Low heme also leads to an accumulation of ALA, which is neurotoxic and induces formation of free radicals (18, 19).

Total inhibition of ALAD in blood cells, reduction of hemoglobin in blood, and anemia have been observed in men with blood lead levels around 3 μmol/l and in women and children with lower levels. Slight effects on hemoglobin concentration and hematocrit (regarded as harmful effects) have been reported at group average blood lead values around 2 – 2.5 μmol/l (18, 19). Some inhibition of enzymes in red blood cells/bone marrow can occur at much lower exposures, however. In one study (13), ALAD activity in red blood cells and ALA content in plasma, blood and urine were reported to be significantly correlated to blood lead level in workers with a group average blood lead level around 0.8 μmol/l. The blood level that can result in "abnormal" changes in ALA-related parameters in 10% of a group (benchmark dose) was calculated, and the result (based on that portion of the group that had blood lead levels below 1.9 μmol/l) indicated a reduction of ALAD activity in red blood cells at 0.13 μmol/l and an increase of ALA in plasma at 0.16 and in blood at 0.2 μmol/l (13). At somewhat higher blood lead levels, inhibition of other enzymes, including pyrimidine-5´-nucleotidase (P5N) was noted. Some inhibition of P5N has been reported at blood lead levels around 0.3 μmol/l. The clinical relevance of such small effects on heme synthesis and nucleic acid metabolism, however, is not clear. Nor is it known whether similar enzyme inhibition occurs in other tissues at similarly low lead exposures. This weak inhibition can thus not be regarded as a critical effect (10, 18, 19).

Kidneys

Lead exposure can cause a deterioration of renal function, characterized by glomerular and interstitial tubular changes that can result in chronic kidney failure. These severe effects occur after high and prolonged exposure. Even with advanced kidney damage there is only mild and non-specific proteinurea (18, 19). The data are unclear with regard to effects on glomeruli at lower exposures. Limited data suggest a possibility of effects on glomerular filtration rate (GFR) in groups of workers with average blood lead levels around 2 μmol/l, though the data are difficult to interpret (18, 19). There are also population studies indicating a correlation at low exposure levels between blood lead and parameters such as creatinine clearance, serum cystatin C, serum urate, blood urea nitrogen and serum creatinine. These effects have been seen in groups with average blood lead levels around 0.5 μmol/l – even lower in a couple of studies. The data may indicate an effect on GFR. A problem with this interpretation is that the relationship might be the reverse: i.e. reduction of the GFR for other reasons may have given rise to the increase in blood lead (19).

In several studies, correlations between lead in blood and bone and effects on proximal tubuli (elevated serum levels of urate and increased urinary excretion of

low-molecular proteins and lysosomal enzymes) have been reported at low lead exposures. These effects have been seen in occupationally exposed groups with group average blood lead values of around 1.5 μmol/l or higher. Limited data also suggest some slight effects of this nature in children with blood lead levels around 0.5 μmol/l. Effects on proximal tubuli due to cadmium exposure may be a confounding factor in some of these studies, but for other studies this risk is considered minimal (18, 19).

Lead also affects the metabolism of vitamin D and calcium, probably through an effect on the kidneys. These effects have been observed in children at blood lead levels around 0.75 – 1 μmol/l. Adults are apparently less sensitive (18).

It is not known whether current exposure or long-term exposure (years or decades) is more relevant for kidney damage. Nor is it clear whether there is a correlation between effects registered in some sensitive urine tests and later clinical chronic kidney disease (18, 19). The health relevance of slight enzymuria, for example, is unknown. There is some information suggesting that damage is reversible if exposure is stopped. Some data suggest that *ALAD* genotype can play some role in determining the nephrotoxic effects of lead, with greater vulnerability in persons having the $ALAD^2$ genotypes (19).

Heart and circulatory system

Exposures that raise the blood lead level above 5 μmol/l in adults or 3 μmol/l in children are often associated with direct toxic effects on the heart muscles (18). Reduced heart rate variability has been reported at average blood lead values around 1.5 μmol/l (discussed further under *Nervous system*).

Lead can also cause a rise in blood pressure, which has been demonstrated in both humans and animals. Elevated blood pressure was reported in early studies of highly exposed workers, and in these cases was often ascribed to lead-induced kidney damage. The picture is more ambiguous in recent studies of workers, who have lower exposures, but there may be effects on blood pressure at group average blood lead values around 1.5 – 2 μmol/l. Further, indications of a blood pressure increase at even lower average blood lead levels (around 0.4 μmol/l) have been found in many epidemiological studies of the general population. Available information suggests that the effect of increasing blood lead on blood pressure is relatively less at high blood lead values than at low ones. The mechanisms behind the effect on blood pressure at low blood lead levels may not be the same as those operating at high levels, where it is often associated with kidney damage. *ALAD* genotype also seems to cause individual differences in sensitivity. However, it is still a question of small increases in blood pressure, and a causal relationship has not been established with certainty. High blood pressure is a known risk factor for cardiovascular and cerebrovascular diseases. Elevated risk of cerebrovascular disease has been indicated in some studies, especially among workers with high exposure to lead (18, 19).

Digestive tract

Lead affects the digestive tract and can cause both constipation and diarrhea, nausea, loss of appetite and stomach cramps. Gastrointestinal effects occur at high exposures, usually at blood lead levels of 3 μmol/l or higher (18).

Endocrine system

In groups with occupational exposure to lead and average blood lead levels around 1.5 – 2 μmol/l, there are some indications of effects on the hypothalamus-pineal-thyroid/adrenal axes. A correlation between blood lead and elevated serum prolactin has been reported in some studies; it may be an early indication of neurotoxicity (18, 19).

The immune system

Lead has a demonstrated immunosuppressive effect. Effects on humoral and cellular immunity, but no indication of a strong immunotoxic effect, have been observed in groups of lead workers with average blood lead levels around 2 μmol/l or higher. Increased susceptibility to infections has been reported in a few studies (18, 19).

Genotoxicity

There are little data indicating that lead (except for lead chromate) can have a direct genotoxic effect. However, there are several studies indicating DNA damage via non-genotoxic mechanisms, with a consequent increase in cancer risk. For example, lead can interfere with DNA repair, defense against free radicals, and metabolism of various genotoxic substances. Lead has a clastogenic effect and induces chromosome aberrations. Elevated occurrences of chromosome aberrations, micronuclei and sister chromatid exchanges in peripheral lymphocytes have been reported in lead workers at average blood lead levels of about 1.5 – 2 μmol/l or higher. An increase of structural aberrations in chromosomes is associated with an increase in cancer risk (18, 19).

Carcinogenicity

Animal studies have demonstrated that some lead compounds can have a carcinogenic effect. The IARC assessment published in 1987 stated that there was "sufficient evidence" for regarding inorganic lead compounds as carcinogenic to animals. Existing epidemiological studies of exposed workers, however, generally did not support this data despite the fact that exposures in many of them had resulted in blood lead levels above 3 μmol/l. The IARC therefore concluded that, for humans, the evidence of carcinogenicity was inadequate; the general classification of inorganic lead and lead compounds was therefore "possibly carcinogenic to humans" (Group 2B) (18). More recent data have provided indications that lead is carcinogenic to humans as well, but there is still no definite

proof. A slightly elevated risk of cancer has been noted in some newer studies, but not in others. Factors such as choice of study group, smoking habits and other exposures make it difficult to draw definite conclusions from this material (19).

Reproduction

Effects of lead exposure on reproduction have been investigated in numerous animal experiments. Pre- and/or postnatal exposure of females can probably disrupt hypothalamus-pineal-ovary-uterus function; one reported result was disruption of the menstrual cycles of monkeys. Injection of high doses of lead during gestation has been found to cause resorption of the embryos, low birth weights, malformations and increased perinatal mortality. Long-term, low-level exposure has been reported to affect development of the central nervous system (CNS). Abnormal behavior and morphological changes in the brain have been observed in primates at doses having no effect on the mothers. Disturbances in heme metabolism have also been observed in the fetuses. Experimental exposure *in utero* has been reported to reduce fertility of females (18), and effects on males have also been shown. Lead exposure can disrupt endocrine functions in males and – probably as a consequence of that, but also because of a direct toxic effect on the testes – affect sperm. Reduced fertility and lower birth weights/survival rates have also been documented in young of male animals exposed to lead (18).

There is less abundant information on humans, but it indicates that lead has several types of effects on reproduction. Limited data suggest a connection between higher blood lead and somewhat later menarche in girls. Longer "time to pregnancy" was also reported in one study (19). Older literature contains reports of spontaneous abortions/stillbirths in women exposed to high levels of lead. It is not clear whether such effects can be observed at lower exposure levels, but there are some data suggesting an effect at blood levels as low as about 0.5 μmol/l. Available information, however, hardly indicates greater numbers of malformations in the fetuses of women exposed to lead (18, 19), although some studies have shown other effects on fetuses. These include disturbances in heme synthesis, shorter gestation time, and lower growth and birth weights. Slight effects on fetal heme metabolism have been observed in groups of women with average blood lead levels of 0.5 μmol/l (18, 19). In some studies, inverse correlations between blood lead and birth weight/length/head circumference are reported for groups of mothers with average blood lead values of <0.5 μmol/l, and in a few studies as low as 0.1 μmol/l, but other risk factors, under/overcontrolled in the statistical model, may have affected these results (18, 19). Lower prenatal growth was shown by regression analysis in a study of a group of mothers with blood lead levels of 0.01 – 0.23 μmol/l (median 0.055) in week 36 of gestation and 0.004 – 0.59 μmol/l (median 0.054) measured in umbilical blood (14). A lead increase of 0.054 μmol/l in umbilical blood was associated with a reduction of 100 g in birth weight, 0.5 cm in birth length and 0.25 cm in head circumference. A correlation between high blood lead levels in the mother during the third trimester

and small head circumference in the child at six months of age was also seen in a study of Mexican mothers with a group average of about 0.4 μmol/l. An elevation of blood lead levels in the mothers (week 36 of gestation) from 0.05 to 1.7 μmol/l was estimated to reduce head circumference at six months of age by 1.9 cm (16). In other studies of Mexican mothers with a group average of about 0.3 μmol/l in umbilical cord blood, biomarkers for lead (primarily bone lead) were negatively correlated to growth parameters such as birth weight, length and head circumference (5, 6).

Lower scores in various psychological tests, as well as less acute hearing, have also been reported in children (Table 2). Slight CNS effects have been reported in groups of children at average blood lead values (pregnant women/fetuses/infants) of about 0.5 μmol/l, and the effects seem to be at least partially irreversible (18, 19). Some studies indicate slight CNS effects in children at blood levels lead below 0.5 μmol/l, but there are numerous methodological problems (e.g. effects of other risk factors under/overcontrolled in the statistical models) (18, 19). In one study (4), a doubling of lead in umbilical blood (e.g. from 0.24 to 0.5 μmol/l) was correlated to somewhat lower scores in a mental development test given at age 2, whereas blood lead levels measured at ages 1 and 2 had no predictive value. This study also reported an inverse correlation between maternal bone lead (measured within 4 weeks after parturition) and results on the development test. In a prospective study made in the Balkan states, blood lead levels were measured prenatally and at six-month intervals from birth until 10 to 12 years of age. A doubling of average lifetime values of blood lead (measured from birth onward), e.g. from 0.14 to 0.3 μmol/l, was associated with a slight reduction in IQ at age 10 – 12. There was reported to be a stronger correlation between IQ and skeletal lead in these children (20). In a meta-analysis based on 8 different studies, it was concluded that an increase of average blood lead from 0.5 to 1 μmol/l yielded a 2.6 point reduction in IQ (17). Children whose blood lead levels never rose above 0.5 μmol/l during this monitoring period had at 10 years of age IQ values that were inversely correlated to blood lead values at age 2. It was also reported that an inverse correlation existed at blood lead levels below 0.24 μmol/l and that no threshold value could be established (1, 2). In another study, there was a strong and significant inverse correlation between blood lead and IQ at ages 3 and 5 in children who in repeated measurements had never had blood lead levels above 0.5 μmol/l. Using a non-linear model, it was calculated that an increase in blood lead from 0.05 to 0.5 μmol/l would decrease IQ by 7.4 points. The calculated reduction of IQ was lower for the same blood lead increase when initial levels were higher (3). IQ reductions proportionally greater at low blood lead levels than at high ones have also been reported in other studies (3). Lead exposure, however, explains only a few percent of the variation in IQ (9).

There are also some data on lead-exposed men. A correlation between lead content in sperm and in blood has been reported in lead workers. There are also indications that occupational exposure to lead has some effects on the

hypothalamus-pineal-testes axis, sperm quality and possibly male fertility in groups of workers with average blood lead values of 1.5 – 2 μmol/l and above. Other effects reported in some studies of lead-exposed men are reduced libido, elevated risk of miscarriage in their wives, and reduced birth weights in their children. Selection and other factors make it extremely difficult to interpret these studies, however (18, 19).

Dose-effect / dose-response relationships

Limited and uncertain data indicate negative effects on prenatal growth at average blood lead values (mothers/fetuses) as low as 0.1 μmol/l, i.e. at levels found in the Swedish populace, and lower than those found in Swedish lead workers. Effects on the central nervous systems of children have been reported at blood lead levels below 0.5 μmol/l. It is not known whether the CNS effects at such low blood lead levels are due primarily to the mother's exposure before the child was born or to the child's postnatal exposure. It should be noted that lead accumulates in bone and is liberated during pregnancy and lactation, so the mother's lead exposure earlier in life also affects the risk.

Effects on blood pressure have been reported in large epidemiological studies of the general population, with a marginal increase at average blood lead levels as low as about 0.4 μmol/l. Such an increase in blood pressure may imply some increase in risk for strokes and heart disease. Some data from population studies may also indicate an effect on kidneys at average blood levels of about 0.5 μmol/l, although these data are difficult to interpret. More definite data indicate that slight effects on kidneys can appear in occupationally exposed persons at group blood lead averages of about 1.5 μmol/l. Effects on the nervous system and endocrine system have been reported at the same average blood lead levels, and effects on hemoglobin concentration, immune system and sperm quality are reported at about 2 μmol/l. Some data also suggest increased DNA damage at group blood lead averages around 1.5 – 2 μmol/l. Correlations between blood lead levels and effects observed in humans are shown in Table 2.

Conclusions in most of the studies are based on differences between groups with different exposures (average values/median values), which makes it difficult to identify a "no observed adverse effects level" (NOAEL) or a "lowest observed adverse effect level" (LOAEL). Methodological problems such as lack of sensitivity in the effect measurements and inadequate control of other risk factors can also occur, particularly with low blood lead levels. Add to this the wide variation in sensitivity to lead (due partly to genetic predisposition) and our relative ignorance regarding the reversibility of some effects. In some cases it is difficult to judge whether subtle, sub-clinical effects, identified with sensitive methods, constitute a genuine risk to a person's health (and thus are relevant here). The relationship between earlier exposures or exposure peaks and the appearance of harmful effects is also difficult to assess (18, 19).

Blood lead is not an ideal measure of exposure, although it is still regarded as the most useful for assessing dose-effect relationships – mostly because of the abundant documentation. A single blood lead value is a poor measure of earlier exposure. Cumulative blood lead or bone lead may be a better measure of long-term exposure. Other limitations on using blood lead as an exposure measure include the fact that blood becomes saturated at higher exposure levels and that, particularly at very low levels, analysis methods may have a high margin of error. Biological monitoring of lead exposure, however, has many advantages over air monitoring. It compensates for variations in respiration and in particle size and solubility of the particulate lead compounds, it covers all paths of uptake, and it also reflects non-occupational exposure. At a given air lead concentration, blood lead levels can vary with lead compound (solubility), particle size and individual physiological factors. It is thus difficult to translate a blood lead value to an air lead value (18, 19).

Conclusions

The critical effects of occupational exposure to lead are judged to be its effects on fetuses and breast-fed babies. There are several studies reporting inhibited growth and effects on the central nervous system in groups of children with average blood lead values (pregnant women/fetuses/babies) in the range 0.1 – 0.5 μmol/l. It is not clear, however, whether the effects on the central nervous system are due primarily to the mother's exposure. It should be remembered that lead accumulates in bone and is liberated during pregnancy and lactation, meaning that the lead exposure of the mother earlier in life is also relevant to the risk. In the Swedish population blood lead levels are about 0.2 μmol/l for men and about 0.15 μmol/l for women. Effects in fetuses and breast-fed babies may exist around these levels.

Effects on blood pressure are reported in large population studies, with a marginal increase at average blood lead levels of about 0.4 μmol/l. An increase of this nature may mean some increase in risk of stroke and heart disease. Effects on kidneys, nervous system and endocrine systems, as well as DNA damage, have been reported in occupationally exposed groups with average blood lead levels of 1.5 μmol/l. Effects on hemoglobin concentration, immune system and sperm quality have been reported in groups with average blood lead values around 2 μmol/l. Lead is carcinogenic to experimental animals, but there is only limited evidence that it is carcinogenic to humans.

There is no simple relationship between levels of lead in air and in blood, and it is therefore not possible to give an air lead concentration for the critical effects.

Table 2. Dose-effect relationships (LOEL – lowest observed effect levels) between lead in blood (averages in the studied populations) and effects on humans (19).

Organ	Effects	Occupationally exposed (μmol/l)[1]	General population	
			Adults (μmol/l)[1]	Children (μmol/l)[1]
Nervous system				
Central	Encephalopathy	>4.0	>4.0	>4.0
	Slight symptoms	1.5 - 2.0	-	-
	Neuropsychological	1.5 - 2.0	-	<0.5[2]
Peripheral	Symptoms	1.5	-	-
	Neurophysiological	1.5	-	-
Complex effects	Cerebral reaction potential	1.5	-	-
	Balance	1.5	-	-
	Hearing	-	-	0.5
Autonomic	Heart rate variability	1.5	-	-
Blood	Anemia	>3.0	>3.0	>3.0
	Hemoglobin concentration	2.0 - 2.5	-	-
	Heme metabolism	0.1 - 0.3	-	-
	Nucleotide metabolism	0.3	-	-
Kidneys	Tubular	1.5	-	0.5 ?
	Glomerular	2.0 ?	0.5 ?	0.5 ?
Cardiovascular	Blood pressure	1.5 - 2.0 ?	0.4	1.8 ?
	Heart rate variability	1.5	-	-
Endocrine system[3]	Hypothalamus/pineal/ thyroid/adrenal axes	1.5 - 2.0	-	-
Immune system	Immune suppression	2.0	-	-
Mutagenicity	Chromosome aberrations, SCE, micronuclei	1.5 - 2	-	-
Reproduction				
Women	Miscarriage	?[4]	0.5 ?	-
	Fetal growth	-	0.1 ?	-
	Neuropsychological effects	-	-	<0.5[2]
Men	Endocrine function	1.5	-	-
	Sperm quality	2.0	-	-
	Fertility	2.0 ?	-	-
Digestive system	Constipation, stomach cramps	>3.0	>3.0	>3.0

? = Limited data, inconsistent results and/or possible/probable confounding factors
– = Not relevant or not sufficiently studied
[1] The interval represents several different studies
[2] Uncertain whether the effects are primarily due to pre- or postnatal exposure
[3] Not including reproduction
[4] Levels not identified, probably high

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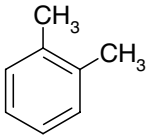
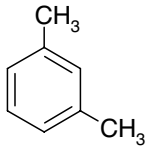
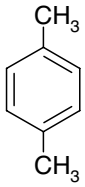
Consensus Report for Xylenes

September 14, 2005

This Report is based primarily on a document from the IPCS (42) and on articles published prior to 2005. The Criteria Group published an earlier Consensus Report for xylene in 1981 (50).

Chemical and physical data

	o-xylene	*m*-xylene	*p*-xylene
CAS No.:	95-47-6	108-38-3	106-42-3
Synonyms:	1,2-dimethylbenzene	1,3-dimethylbenzene	1,4-dimethylbenzene
	o-methyltoluene	*m*-methyltoluene	*p*-methyltoluene
	1,2-xylene	1,3-xylene	1,4-xylene
	o-xylol	*m*-xylol	*p*-xylol
	ortho-xylene	*meta*-xylene	*para*-xylene
Structure:			
Formula:	C_8H_{10}	C_8H_{10}	C_8H_{10}
Molecular weight:	106.16	106.16	106.16
Density: (g/cm^3, 25 °C)	0.876	0.860	0.857
Boiling point: (°C, 101.3 kPa)	144.4	139.1	138.3
Melting point: (°C, 101.3 kPa)	-25.2	-47.9	13.3
Vapor pressure: (kPa at 20 °C)	0.66	0.79	0.86
Distribution coefficients:			
$P_{oil/air}$	4360	3842	3694
$P_{blood/air}$	31	26	38
$P_{olive\ oil/blood}$	140	146	98
$P_{octanol/water}$	3.12	3.20	3.15
Solubility in water: (mg/l)	142	146	185
Conversion factors: (25 °C, 101.3 kPa)	1 ppm = 4.35 mg/m^3; 1 mg/m^3 = 0.23 ppm		

Xylene is an aromatic hydrocarbon. At room temperature it is a clear, flammable liquid with a pleasant odor. The odor threshold for xylene in air is about 1 ppm (4.35 mg/m^3) (42). Xylene occurs in three isomeric forms: *ortho-*, *meta-*, and *para-*xylene. All three isomers are soluble in organic solvents such as ethanol, diethylether, acetone and benzene. Industrial grade xylene is 40 – 60% *m*-xylene, with ethylbenzene, *o*-xylene and *p*-xylene each accounting for a further 10 – 20%.

Xylene is distilled primarily from petroleum and to a lesser extent from coal. About 92% of mixed xylenes is used in gasoline. The *p*-xylene isomer is used in production of dimethyl terephthalate film and phthalic acid diisooctyl ester for production of polyester fibers and films. Most *o*-xylene goes into production of phthalic acid anhydride, which is used to make phthalate plastic, and *m*-xylene is used in production of isophthalic acid for making polyester plastic. Industrial (mixed) xylene is used mostly as a solvent in production of paints, pesticides, pharmaceuticals, rubber and plastic, and in the perfume and leather industries (42).

Workers in the chemical and paint industries and workers who use products containing xylenes (e.g. painters, printers) can be occupationally exposed, but occupational exposure to xylene alone is rare. Exposure levels in histology laboratories can range from 20 to 70 ppm (90 – 300 mg/m^3) (80). Exposure is usually mixed, however: other organic solvents such as toluene, ethylbenzene, n-hexane and isopropanol are often present as well. A typical exposure level for one workshift in various kinds of painting shops is below 5 ppm (20 mg/m^3). Around printing presses and in chemical plants there may be brief exposures of up to 100 – 200 ppm (400 – 900 mg/m^3) (9, 42, 89), and around installation of flooring concentrations up to 7000 ppm (30,000 mg/m^3) may occur (62).

Uptake, biotransformation, excretion

The primary exposure route for xylenes is inhalation of xylene vapors. When volunteers were exposed to different xylene isomers in concentrations up to 200 ppm (870 mg/m^3), relative uptake was reported to be 59 – 64% (75, 84). Since the relative uptake is independent of physical activity, the absolute uptake increases in proportion to the increase in workload and pulmonary ventilation (75). Blood levels also increase with workload. After two hours of exposure to 50 ppm (217 mg/m^3) *m*-xylene with a workload of 50 W, the maximum concentration in blood was 11.2 μmol/l (about 1.2 mg/kg) (24). After 30 minutes of exposure to 200 ppm (870 mg/m^3) xylene (mixed) while resting, blood level was 1.6 mg/kg (about 15 μmol/l) (98). In this study, blood level rose to 7 mg/kg (about 66 μmol/l) with 90 minutes of exposure to 200 ppm and a 50 W workload.

Skin uptake of liquid xylene was quantified by having subjects immerse their hands in liquid *m*-xylene for either 15 or 20 minutes. Absorption, calculated from the amount of *m*-methylhippuric acid excreted in urine, was 2 – 2.5 μg/cm^2/minute (54, 72). If the ECETOC criteria for skin notation are applied (16), i.e. exposure of 2,000 cm^2 skin for 1 hour, the dose absorbed through the skin would be 240 –

300 mg, equivalent to 24 – 30% of the dose absorbed by inhalation at 200 mg/m^3 (the present Swedish exposure limit), assuming inhalation of 10 m^3 of air during an 8-hour shift and uptake of 50%. Skin exposure to liquid xylene can thus result in significant absorption.

Skin uptake of xylene in vapor form was studied in 5 men who were exposed to 300 or 600 ppm (1305 or 2610 mg/m^3) xylene for 3.5 hours. Total absorption of *m*-xylene was about the same as with inhalation exposure to about 10 ppm (44 mg/m^3) for the same amount of time (74). This indicates that with whole-body exposure the dermal contribution to total uptake would be about 1.7 – 3.3% of the inhaled dose. In one study (56), the contribution of dermal uptake, estimated with use of a physiologically based pharmacokinetic model, was 1.8%. In a later study of dermal uptake, the contribution of xylene in vapor form was calculated to be 0.2% (47). These calculations were based on a reference inhalation exposure of 30 minutes at 19 mg/m^3 (4 ppm) and exposure of the lower arm and hand to *m*-xylene for 20, 45, 120 or 180 minutes (six men). The xylene concentration was measured in exhaled air.

All the xylene isomers are absorbed when administered orally to rats. The maximum concentration in blood was reached 4 hours after single doses (by gavage) of 0.5 – 4 g *m*-xylene or 1.1 g *p*-xylene/kg body weight (42).

Xylene is distributed rapidly to body organs by the blood. For organs with rich blood flow it takes only a few minutes to reach equilibrium, whereas it takes some hours for muscle tissue and several days for fat (76). Xylene has high affinity for adipose tissue. The measured half time for xylene in human subcutaneous fat was about 58 hours (20). After 5 to 6 days of repeated exposure to 90 – 200 ppm (413 – 870 mg/m^3) xylene, about 3.7 – 8.0% of the total lung uptake was found in adipose tissue (20, 75).

Xylene has been shown to pass the placental barrier in both humans and laboratory rodents (14, 29, 65, 92).

Autoradiography of male mice that had inhaled ^{14}C-labeled xylene showed an accumulation of non-volatile metabolites, primarily methylhippuric acid, in the olfactory bulb (30). The accumulation of methylhippuric acid in the olfactory bulb may indicate transport from nasal mucosa to the olfactory bulb, but it might also be explained by blood transport.

About 95% of the xylene that is absorbed by humans is excreted as metabolites in urine, and only a little is eliminated unchanged in exhaled air (73). The clearance of *p*-xylene from the blood has been calculated to be 2.6 liters/kg/hour at 20 ppm (87 mg/m^3) and 1.6 liters/kg/hour at 70 ppm (304 mg/m^3) – on the same order of magnitude as hepatic blood flow, which indicates high metabolic capacity (94).

The main biotransformation pathways for xylene are summarized in Figure 1. Xylene is transformed primarily to methylbenzoic acid via microsomal side-chain oxidation. This is followed by binding to glycine, forming methylhippuric acids which are excreted in urine. In humans, the glycine conjugation can be saturated at high xylene concentrations: this has been calculated to occur at 270 ppm

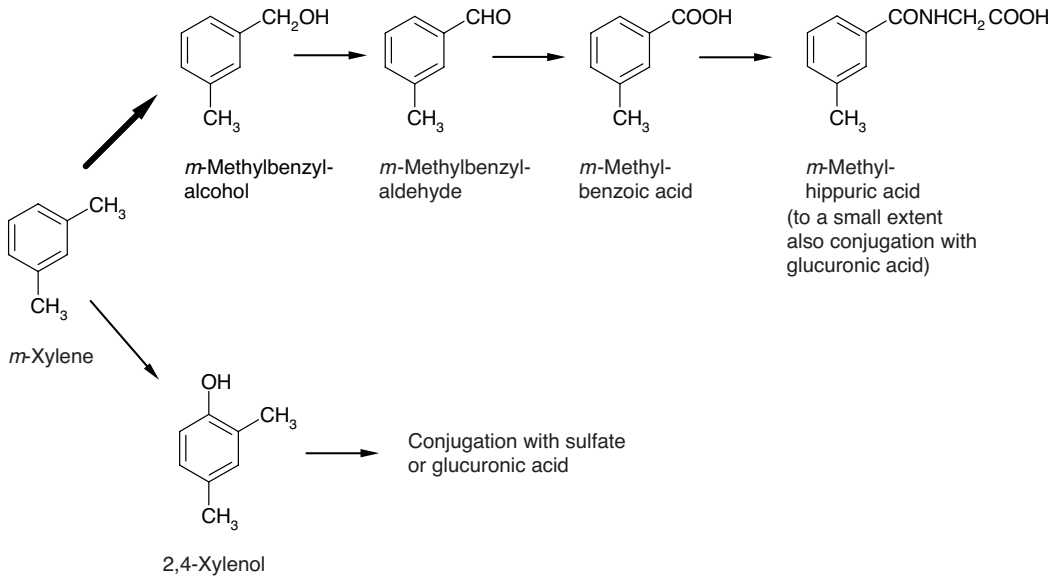


Figure 1. Metabolism of *m*-xylene (modified from Reference 73).

(1174 mg/m^3) with moderate physical labor and at 780 ppm (3393 mg/m^3) during rest (71). Aromatic oxidation of xylenes to dimethylphenols (Figure 1) accounts for only 1 – 3% of total metabolism (22, 73). Small amounts of glucuronide esters of methylbenzoic acid and trace amounts of methylbenzyl alcohol have been identified in human urine (6, 22, 68).

Most of the studies of xylene metabolism have been made with rats. In rats, as in humans, the primary metabolic pathway is oxidation of one of the methyl groups (18). Unique to rats, however, is that a relatively larger proportion of the xylene is metabolized to methylmercapturic acid, a few percent after exposure to *m*- and *p*-xylene and 10 – 20% after exposure to *o*-xylene (95, 96). It is possible that xylenols and their reactive intermediates are formed via aromatic oxidation, but if so the amounts are extremely small (45).

Two excretion phases, with half times of 3.6 and 30 hours, have been identified for methylhippuric acid in urine of occupationally exposed subjects (19).

In a study in which volunteers inhaled 50 ppm *m*-xylene, there were no observable sex differences in uptake, biotransformation or excretion of xylene (24).

Biological measures of exposure

Methylhippuric acid in urine is commonly used as a biomarker for xylene exposure. The analyses are usually made with liquid chromatography and UV detection. Methylhippuric acid is not found in unexposed people. Excretion of methylhippuric acid is proportional to exposure levels at both low (<15 ppm) (44) and higher (up to about 100 ppm) (38) xylene levels. It is stated in a review article that 8 hours of exposure to 100 ppm (435 mg/m^3) corresponds to 1.5 – 2 g methylhippuric acid/g creatinine in urine samples taken after a workshift (53).

This figure is an average from several studies. Measurements of xylene in blood, urine and exhaled air are also reliable indicators of xylene exposure (8, 86). These analyses are usually made with gas chromatography.

Germany has a legally binding biological exposure limit (BAT: *Biologischer Arbeitsstoff-Toleranz-Wert*) of 2000 mg/l for methylhippuric acid in urine after a workshift, and the ACGIH in the U.S. recommends a biological limit (BEI: Biological Exposure Index) of 1.5 g/g creatinine after a workshift.

Toxic effects

Human data

Neurological and psychological changes have been observed in workers exposed to solvent mixtures containing xylene (42). Common acute symptoms are headache, fatigue, dizziness and intoxication. Long-term and/or heavy exposures can lead to severe brain damage, often referred to as psychoorganic syndrome (POS) or chronic toxic encephalopathy, which is characterized by deterioration of memory, concentration and learning ability, and emotional symptoms such as fatigue and depression (52, 61, 69). This type of damage has commonly been associated with exposure to solvent mixtures. Since there is usually no quantitative information on exposures, it is impossible to describe a dose-response relationship.

From a study population of 994 workers exposed to solvents, 175 workers were chosen on the basis of whole-day measurements (personal monitors) showing exposure to a solvent mixture containing ≥70% xylene. These workers had been exposed for an average of 7 years. The xylene concentration was 14 ppm (geometric mean; 21 ppm arithmetic mean), with individual values up to 175 ppm (8-hour time-weighted averages). An elevated prevalence of symptoms was found in the exposed workers when they were compared with the control group (n = 241 unexposed workers). The symptoms comprised CNS effects (nausea, anxiety, forgetfulness, loss of concentration) and irritation of eyes, nose and throat. There was no observed effect on the number of white blood cells or on liver and kidneys (89). In the same study population there were 233 workers exposed to a mixture of 4 ppm xylene (individual values up to 103 ppm) and 3 ppm toluene (maximum value 203 ppm) (geometric means, 8-hour time-weighted averages). The prevalence of CNS symptoms in this group was higher than in the controls (n = 241) (9). These two studies are difficult to evaluate because of shortcomings in design, including the formulation of the questionnaire and the fact that only a few symptoms showed the anticipated dose-response relationship.

EEGs were used to study "event-related potentials" in laboratory personnel exposed to xylene and formaldehyde. There was a correlation between *m*-methylhippuric acid in urine and latency time (55). This study is not described in sufficient detail to allow any definite conclusions. For example, it is impossible to determine whether the subjects were still being exposed during the EEG recording. Exposure to formalin may also have played some role.

In a report on 38 occupationally exposed workers with acute xylene poisoning, CNS effects (headache, nausea, dizziness), gastrointestinal symptoms (nausea, vomiting), liver and kidney damage, and irritation of eyes, nose and throat were common symptoms (5). Headache, dizziness and nausea were observed after exposure to about 700 ppm (3031 mg/m^3) xylene. Exposure lasting about 1 hour occurred in a hospital laboratory where 1 liter of xylene was poured into a sink. Symptoms were reported by 9 of 15 exposed workers, and lasted from 2 to 48 hours (48).

About 20 studies with experimental exposure to *o*-, *m*-, *p*-xylene or to xylene mixtures have been made with human volunteers. Most of them were made at the Institute of Occupational Health in Helsinki. In brief, these studies show that temporary CNS effects appear after a few hours of exposure to about 100 ppm. At this level, effects on reaction time, coordination, memory and balance were seen in several of the studies (15, 82, 83). Savolainen *et al*. (82) compared effects of constant and fluctuating xylene concentrations in a small group of volunteers (n = 6) exposed 6 hours/day for two weeks. The effects were more pronounced at the beginning of the exposure and with fluctuating exposure than they were with constant exposure having the same time-weighted average (100 ppm). In another study (83), eight volunteers were monitored during six days of exposure either to a constant 90 ppm (392 mg/m^3) or to concentrations fluctuating between 64 ppm (278 mg/m^3) and 200 ppm (870 mg/m^3) with a time-weighted average of 92 ppm (400 mg/m^3). They did light physical work daily, 4 x 10 minutes with a 100-W load on a bicycle ergometer. There were observable effects on balance, coordination and reaction time at the constant exposure. In another study with 10 volunteers, it was found that four hours of exposure to 100 ppm (435 mg/m^3) xylene (undefined composition) resulted in lower performances on a memory test and two different tests of reaction time (15).

Sixteen men were exposed to 70 ppm (304 mg/m^3) *p*-xylene for 4 hours: no effect on performance in psychological tests and no irritation of eyes, nose or throat was reported after the exposure (1).

In an exposure chamber study, 56 healthy volunteers (28 women and 28 men) were exposed for 2 hours, on two occasions, to either 50 ppm *m*-xylene or pure air. Before, during and after the exposures they rated their discomfort levels on a questionnaire (Visual Analog Scale). Symptoms that were rated were discomfort in the eyes, nose, throat or airways, breathing difficulty, solvent smell, headache, fatigue, nausea, dizziness and feeling of intoxication. All symptoms increased significantly with the xylene exposure ($p \leq 0.05$, Wilcoxon signed rank test) at some time (after either 60 or 118 minutes of exposure) in one or both sexes. The differences in symptom ratings before and during the exposure were small, however (3 – 12 mm, or "hardly at all" to "somewhat") except for solvent smell (34 – 45 mm, "somewhat" to "rather"). Sex difference was significant only in ratings of discomfort in throat and airways. Other effects measured in this study were lung function, blinking frequency, nasal swelling, color vision and inflammatory markers in nasal lavage fluid. In these measures, no effect of the xylene exposure was seen (23).

A study from 1943 reports irritation of eyes, nose and throat in 10 persons after they were exposed to 200 ppm xylene (composition not given) for 3 to 5 minutes (66).

Four of six persons reported eye irritation after 15 minutes of exposure to 460 or 690 ppm (2000 or 3000 mg/m^3) of a solvent mixture containing 7.6% *o*-, 65% *m*-, 7.8% *p*-xylene and 19.3% ethylbenzene. One of the six reported eye irritation at 230 ppm (1000 mg/m^3), and no irritation was reported at 110 ppm (500 mg/m^3) (7).

Volunteers who immersed their hands in liquid xylene reported burning and stinging sensations, and their hands became red (erythema) within 10 minutes. The symptoms disappeared within 10 to 60 minutes after they removed their hands (21, 54, 72). One case of contact urticaria due to xylene exposure has been reported (97).

Effects on liver have been reported in workers exposed to xylene, but these studies contain no quantitative exposure data. In one case report, a 42-year-old painter exposed mostly to xylene had elevated ASAT (aspartate aminotransferase) and ALAT (alanin-aminotransferase) levels in serum and normal γ-GT (γ-glutamyl transferase). He had low alcohol consumption, but a biopsy revealed fatty changes in his liver (17). Fifteen workers in the chemical industry and 8 painters had changes shown by liver tests after several years of exposure to solvents. The liver test results were normalized within three to six weeks after exposure was stopped (85). Of 156 patients (house painters) examined for solvent damage, 23 had elevated aminotransferases in serum. Histologic examination of their livers revealed fatty degeneration in 11 of them, and in six of these focal necroses were also seen (13). Of 25 workers in the chemical industry who had been exposed to toluene, xylene, methylethylketone and other solvents, 13 had elevated levels of liver enzymes, γ-GT, serum ASAT and ALP (alkaline phosphatase) (25). Indications that liver damage is more common in house painters than in carpenters were observed in one study (58), whereas another study of 47 workers exposed to 19 ppm (82 mg/m^3 median) xylene showed no effects on liver enzymes in comparisons with unexposed workers (57). Nor was any effect on liver enzymes observed in a study in which painters with an average exposure of 6 ppm xylene (26 mg/m^3) were examined (51).

There is a case-control study of 30 cases (20 to 59 years old) of cirrhosis (diagnosed by biopsy) and 120 randomly chosen controls from the same geographical area. Exposure estimates were based on a questionnaire including job title and solvent exposure (solvent undefined) at work. The result for those who had been moderately exposed for more than 1 year in the most recent 15 years showed an age-adjusted Mantel-Haenszel odds ratio of 4.3 (95% CI: 1.2 – 15). For those with high exposure the odds ratio was 7.7 (95% CI: 1.7 – 48), which indicates that occupational exposure to solvents may cause fatty liver disease (59).

Animal data

Xylene has low acute toxicity with both inhalation and oral administration. For mice and rats, the LC_{50} for inhalation ranges from 4300 to 6000 ppm and the LD_{50} for oral administration ranges from 3.6 to 5.6 g/kg for the different xylene isomers. A dermal LD_{50} of 12 g/kg has been reported for rabbits (42).

For mice exposed to 500 – 4000 ppm (2200 – 17,000 mg/m^3) *m*-xylene, the RD_{50} (the concentration that reduces respiratory rate by 50%) was determined to be 1360 ppm (5900 mg/m^3) (49).

Groups of Mongolian gerbils (4 males and 4 females/group) were continuously exposed to 0, 160 or 320 ppm xylene (18% *o*-, 70% *m*-, 12% *p*-xylene, <3% ethylbenzene, <0.1% toluene) for three months. Four months later, the concentrations of two markers for astroglial cells (GFA and S-100) and DNA were measured in various parts of the brain. In the group exposed to 320 ppm the levels of GFA and S-100 were significantly higher in the frontal cerebral cortex and GFA was higher in the cerebellar vermis, compared with controls. In the anterior part of the vermis the GFA level was significantly higher with the 160 ppm exposure as well. In the posterior part of the cerebellar vermis the DNA concentration was significantly higher than controls after exposure to both 160 and 320 ppm. According to the authors, these results indicate that xylene induces an increase of astroglial cells in certain parts of the brain as an indication of brain damage, and that the damage is irreversible (79).

Male rats (n = 11) were exposed to 100 ppm *m*-xylene 6 hours/day, 5 days/week for 4 weeks. Behavior tests were administered 20 to 60 days after the exposure. Compared with unexposed controls (n = 10), the exposed group showed changed behavior in a "passive avoidance test" (given 39 – 48 days after the exposure), a "hot-plate test" (given 50-51 days after the exposure) and "active avoidance learning (acquisition)" (day 54 after the exposure). According to the authors, these results show that short-term exposure to 100 ppm *m*-xylene yields permanent changes in the behavior of rats. Xylene induced the same behavioral changes as trimethylbenzenes (TMB) (32). The authors suggest that, if xylene and TMB affect the dopaminergic system in the same way as toluene has been shown to do, this might explain the observed changes in behavior. A possible explanation for the effects on behavior may be that xylene induces a stress reaction in the rats. Many solvents, including xylene, have been shown to induce EEG changes similar to those induced by the odor of rat predators such as foxes or weasels. This hypothesis is also compatible with an effect on the dopaminergic system associated with stress reactions (32).

A single application of xylene (unspecified) was slightly irritating to the skin of rabbits and guinea pigs (37). Application of 0.5 ml *p*-xylene to the skin of rabbits for 4 hours under occlusion was judged to meet the EEC criteria for skin irritation (43). Xylene caused erythema and increased capillary permeability in rat skin, a result of liberated histamine and 5-hydroxytryptamine (10). No published data on skin sensitization were found.

Application of 0.05 – 0.5 ml liquid xylene (individual isomers or unspecified mixture) to the eyes of rabbits caused immediate discomfort and spasms in the eyelids, followed by slight irritation of the conjunctiva and slight, temporary corneal necrosis (37). Application of 0.1 ml xylene (unspecified) in rabbit eyes caused slight irritation (46).

In one study, 250 µl *m*-xylene was applied to the backs of rats under occlusion for 1 hour. Skin biopsies taken before and 1, 2, 4 and 6 hours after the beginning of exposure showed increased interleukin-1α (maxima after 1 and 2 hours) and inducible nitric oxide synthase (maximum after 4 hours). According to the authors these markers may reflect the skin-irritating ability of xylene. Histological changes 6 hours after the application (blister formation and granulocyte infiltration) were also observed in the study (33).

Hearing loss in rats exposed to xylene has been demonstrated in several studies (11, 26, 67, 70). In one study the effect was shown after exposure to 800 ppm mixed xylene 14 hours/day, 7 days/week for 6 weeks (70). In another study (67), a slight loss of hearing was demonstrated after exposure to 1000 ppm mixed xylene 18 hours/day for 61 days. In a study by Gagnaire *et al*. (26), only *p*-xylene (6 hours/day, 6 days/week for 13 weeks) yielded hearing loss at 900 ppm ("brain-stem auditory evoked response" was tested). The effect was not seen at 450 ppm *p*-xylene (26). Crofton *et al*. (11) showed that rats exposed to a mixture of xylene isomers, 1800 ppm, 8 hours/day for 5 days, developed hearing loss in the medium-frequency range (8 –16 kHz). This pattern is similar to the one shown by toluene (11).

All three xylene isomers affect the oculomotor nerve, which controls eye movement, after i.v. administration to rats. The threshold in blood for the effect was 1.6 – 1.9 mmol/l (88). Nystagmus has also been reported in rabbits exposed to *m*-xylene. The effect on the nerve was observed at blood concentrations above 0.3 mmol/l (3). Humans would reach this blood concentration with light work (50 W) at an air concentration of about 1000 ppm (4350 mg/m^3) (see Biological measures of exposure).

Enlarged livers and increased activity of liver enzymes (ASAT, ALAT, ornithine carbamyl transferase) and cytochrome P450 after inhalation exposure to relatively high concentrations of xylene (>1000 ppm, 4 hours/day) have been observed in several studies. Slight changes in hepatocytes and some effect on liberation of catecholamines in the brain have also been observed (42).

Benzene has been shown to induce toxic effects in bone marrow. In comparative studies with benzene, xylene yielded no indications of bone marrow toxicity (73).

Mutagenicity

None of the xylene isomers was mutagenic to *Salmonella typhimurium*. The xylene isomers induced no DNA-mediated toxicity in several strains of bacteria, either with or without addition of metabolic systems (42). Exposure to industrial

xylene, but not exposure to *m*- or *o*-xylene, yielded recessive lethal mutations in *Drosophila* (12). In the same study, it was found that exposing rats to 300 ppm (1300 mg/m^3) 6 hours/day, 5 days/week for 9, 14 or 18 weeks did not induce chromosomal aberrations in bone marrow. Xylene (unspecified) induced no sister chromatid exchanges or chromosome aberrations in human lymphocytes *in vitro* (28). Nor did any of the xylene isomers induce micronuclei in the bone marrow of mice after two intraperitoneal doses (105 – 650 mg/kg b.w.) (64).

Carcinogenicity

Human data

Epidemiological studies have yielded no convincing evidence of an elevated risk of cancer after exposure to xylenes. Gerin *et al*. made a case-control study in Montreal (27) in which 3730 cancer patients and 533 controls were interviewed about occupational exposures (benzene, toluene, xylene and styrene). There were 15 types of cancer cases (not leukemia). Exposure levels were low and there were high correlations between benzene, toluene, xylene and styrene. For most of the cancer types, these substances showed no increase in risk. A somewhat higher OR (5.8, 95% CI: 1.5 – 22.0) was found for xylene and colon cancer. In another study (31), probably of the same material, only occupational exposure and risk of colon cancer was investigated: the risk after exposure to xylene was not significantly elevated (OR 1.9, 95% CI: 0.8 – 4.3).

A study by Anttila *et al*. examines cancer incidence in 3922 men and 1379 women exposed to styrene, toluene or xylene during the 1973 – 1992 period (2). The cancer incidence for the entire cohort was the same as that for the general population. No elevation in cancer risk was seen for xylene exposure. Xylene exposure was determined by measurement of methylhippuric acid in urine.

In one study with 192 cases of glioma and 343 controls, a significantly elevated relative risk was observed for men after exposure to organic solvents including xylene (exposure was classed by an occupational hygienist on the basis of questionnaires): RR 2.6 (95% CI: 1.3 – 5.2) (77); 38% of the cancer cases and 14% of the controls had been exposed to solvents. When the data were analyzed in subgroups based on the type of solvent exposure (self-reported), benzene had an RR of 5.5 (95% CI: 1.4 – 21.3), whereas for xylene (RR 3.3, 95% CI: 0.6 – 18.6), toluene and trichloroethylene there was not a significant increase in risk. The numbers of unexposed and exposed subjects in the subgroups were not reported. No significant increase in relative risk was observed in women, but only 3% of the women with glioma had been exposed.

The IARC has placed xylene in Group 3: “The agent is not classifiable as to its carcinogenicity to humans” (41).

Animal data

Groups of rats, 40 of each sex, were given xylene (unspecified) in olive oil, 500 mg/kg b.w., 4 or 5 days/week for 104 weeks. The controls, 50 animals of each

sex, were given only olive oil. After 141 weeks, when all the animals had died, 13/38 of treated males and 22/40 of treated females were found to have malignant tumors, compared with 11/45 and 10/49 in controls (60). According to the IPCS, it is unacceptable to group all the tumors together for analysis – especially when the animals died of old age (42).

The NTP has made carcinogenicity studies of industrial xylene (9% *o*-, 60% *m*-, 14% *p*-xylene and 17% ethylbenzene) with Fischer-344 rats and B6C3F$_1$ mice. Groups of 50 animals of each sex were given the xylene (in corn oil) by gavage: 0, 250 or 500 mg/kg b.w. (rats) and 0, 500 or 1000 mg/kg b.w. (mice), 5 days/week for 2 years. There were no observed treatment-related increases in tumor incidence when these animals were compared with controls (40, 42).

Effects on reproduction

Human data

Pregnancy outcomes were studied in personnel employed in laboratory work at Gothenburg University between 1968 and 1979. A questionnaire was sent to 782 women, and the response frequency was 95%. Laboratory work (n = 576) was associated with a slight but not significant increase in spontaneous abortions (RR 1.31, 95% CI: 0.89 – 1.91). No differences in perinatal death or prevalence of birth defects were found between babies whose mothers were exposed to solvents and those of unexposed mothers. No data on xylene exposure is given in the study (4).

In a Finnish cohort study of laboratory personnel, no correlation was found between exposure to xylene and birth defects in a case-control analysis, but the power of the study was low. A case-control study of the cohort, however, revealed a significant correlation between spontaneous abortions and exposure to xylene (206 cases and 329 referents, OR 3.1, 95% CI: 1.3 – 7.5). Exposure estimates were based on job descriptions and made by an occupational hygienist. Mixed exposures were common (87).

Animal data

Several studies have reported embryotoxic effects (reduced weight, delayed ossification, increased post-implantation losses) in animals exposed to xylene by inhalation (34, 39, 63, 78, 90, 91, 92, 93). Elevated frequencies of skeletal anomalies (extra ribs and "fused sternebrae") have been reported, but no solid evidence that xylene caused them. Many of these studies are difficult to assess because of unclear and incomplete information on maternal toxicity and exposure conditions.

Hass *et al*. used neuromotor tests and memory and learning tests to study postnatal development of rats after prenatal exposure. Their dams had been exposed for 6 hours/day to 200 ppm industrial xylene (composition not reported) on days 4 – 20 (34) or 500 ppm industrial xylene (19% *o*-, 45% *m*-, 20% *p*-xylene, 15% ethylbenzene) (35, 36), on days 7 – 20 of gestation. It was observed that on

day 21 of gestation the fetuses in the 200 ppm exposure group had a higher frequency of delayed ossification (69%), especially of *os maxillaris*, than controls (9%) (34). After the 200 ppm exposure, on days 22 – 24 after birth, the young were given a neuromotor performance test (Rotarod) in which the time a rat can remain on a spinning rod was measured. A significantly lower time was observed for females on days 22 and 23, and for the males on day 23. There were no indications of maternal toxicity (34). In the follow-up study with 500 ppm exposure the number of tests was increased, and 15 exposed and 13 unexposed litters were tested. No indications of maternal toxicity were observed (feed intake, weight gain, length of gestation, litter size and sex ratios in the litters). The pups of exposed mothers had later development of the "air righting reflex" and on day 28 post-partum they had significantly lower absolute brain weights. A not significant trend to lower performance in the Rotarod test was observed on days 24 – 26. At 12 – 14 weeks of age the pups were tested in the Morris water maze, a test of learning and memory functions in which the rats must find an invisible, submerged platform (1 cm below the surface) in a round basin. The performance of the females in the exposed group was significantly worse than that of controls. In general, the effects were more pronounced in the females (36). The females were further tested at 28 and 55 weeks of age, and on these occasions also they did less well than controls in the Morris water maze, although at 55 weeks the difference was not significant (35).

Pregnant rats were exposed to industrial xylene (15% ethylbenzene, 21% *o*-, 44% *m*-, 19% *p*-xylene), ethylbenzene, *o*-, *m*-, or *p*-xylene (0, 100, 500, 1000 or 2000 ppm) 6 hours/day on days 6 – 20 of gestation. At 1000 and 2000 ppm, the solvent exposures resulted in lower weight gains in the mothers. Corrected weight gain (weight minus weight of uterus with fetuses) and food intake were lower at 1000 and 2000 ppm for ethylbenzene, *o*-, *m*- and *p*-xylene, and at 2000 ppm for industrial xylene. Reduced fetal weights on day 21 of gestation were observed in the two highest dose groups for all the tested substances, and for *o*-xylene and industrial xylene at 500 ppm as well. No indication of teratogenic effects was seen at any exposure (81).

Dose-response / dose-effect relationships

The most important studies of xylene's effects are summarized in Table 1 (human data) and Table 2 (animal data).

For humans, irritation from xylene inhalation has a dose-effect relationship. Four of six volunteers reported eye irritation with 15 minutes of exposure to 460 or 690 ppm (2000 or 3000 mg/m^3). One subject showed symptoms of eye irritation at 230 ppm (1000 mg/m^3) (7). With exposure to 200 ppm xylene (undefined) for 3 to 5 minutes, more than half of the ten subjects reported irritation of eyes, nose and throat (66). No eye irritation was observed at 110 ppm (478 mg/m^3) (7). No irritation of eyes, nose or throat was reported by 16 men who were exposed to 70 ppm (304 mg/m^3) *p*-xylene for 4 hours (1). A significant increase of discomfort in eyes and nose was reported by 56 subjects exposed to

50 ppm *m*-xylene for 2 hours (23). The discomfort levels they marked on the visual analogue scale ranged from "hardly at all" to "somewhat".

The RD_{50} for *m*-xylene (the concentration that reduces respiratory rate by 50%) has been reported to be 1360 ppm (5900 mg/m^3) for mice. The RD_{50} is a measure of sensory irritation of respiratory passages. The ACGIH threshold values based on irritation are on average about equal to 3% of the RD_{50} value. For *m*-xylene this would be about 40 ppm.

Dose-effect relationships have also been observed for acute CNS effects on humans. Several studies in which subjects were exposed to 90 – 100 ppm (392 – 470 mg/m^3) xylene (15, 82, 83) have shown acute CNS effects on reaction times, balance, coordination etc. Four hours of inhalation of 70 ppm (304 mg/m^3) xylene in an exposure chamber had no effect on psychophysiological functions (1). A study by Ernstgård *et al*. (23) reports that marginal but statistically significant increases in CNS symptoms (headache, fatigue, nausea, dizziness and feeling of intoxication) were observed at 50 ppm *m*-xylene. The symptoms were not severe and were marked in the "hardly at all" area on the visual analogue scale.

In two epidemiological studies (9, 89) CNS symptoms (nausea, anxiety, forgetfulness, concentration difficulty) and irritation effects (eye, nose, throat) are reported at average solvent concentrations of 14 and 4 ppm respectively (geometric means). The average exposure levels were low in the two studies, but levels approaching 175 ppm (8-hour time-weighted averages) occurred. These two studies are difficult to assess, largely due to shortcomings in design – especially the formulation of the questionnaire and the fact that only a few symptoms showed the expected dose-response relationship.

Long-term and/or heavy exposure to solvent mixtures containing xylene can lead to chronic toxic encephalopathy in humans, but the dose-response relationship is poorly known.

In animal experiments, effects on the CNS, considered irreversible, have been observed after exposure to 100 ppm *m*-xylene for 4 weeks, and 160 ppm mixed xylene (18% *o*-, 70% *m*-, 12% *p*-xylene, <3% ethylbenzene, <0.1% toluene) for 4 months (32, 79).

In one study of xylene-exposed persons, a significant correlation was observed between xylene exposure and subsequent spontaneous abortions. However, only two cases were exposed to xylene alone (87). Xylene has demonstrated toxic effects on the reproduction of rats. The pups of rats exposed during gestation to industrial xylene (inhalation, 200 or 500 ppm) showed effects on development of the nervous system in various neuromotor, memory and learning tests given on days 22 – 28 after birth. At the higher dose (not tested at the lower dose), demonstrable effects persisted to adulthood, and were more pronounced in the females (34, 35, 36). Lower fetal weights were observed with exposure to 500 ppm *o*-xylene or industrial xylene (81).

Xylene is ototoxic to rats at about 800 ppm (3480 mg/m^3) (70). There are no human studies of ototoxicity due to xylene exposure alone.

Conclusions

The critical effects of occupational exposure to xylene are judged to be irritation and acute effects on the central nervous system. In an experimental study, irritation and CNS effects were reported with exposure to 50 ppm *m*-xylene. More pronounced irritation of eyes, nose and throat have been reported with brief exposure to 200 ppm. In other experiments with human subjects, it was found that exposure to 90 ppm xylene impairs performance on neuropsychological tests. Exposure to 70 ppm did not affect performance on similar tests.

Chronic toxic encephalopathy (memory and concentration problems, depression and fatigue) can occur with prolonged and/or heavy exposure to xylene in mixtures with other solvents. Dose-response relationships are poorly understood, however. In animal experiments, CNS effects considered to be permanent have been demonstrated at exposure to 100 ppm *m*-xylene and 160 ppm industrial xylene. There are thus two independent animal studies supporting the conclusion that chronic CNS effects can arise at 100 – 200 ppm. It is not clear whether these animal data can be translated to neurotoxic effects on humans.

Effects on the development of the nervous system have been demonstrated in the young of rats exposed to 200 ppm industrial xylene during gestation.

Skin contact with liquid xylene causes erythema and a burning, stinging sensation. Repeated skin contact depletes the skin of lipids and results in skin irritation. Skin exposure to liquid xylene can result in significant systemic exposure.

Table 1. Dose-effect relationships observed in studies of persons occupationally exposed to xylene or exposed in an exposure chamber.

Xylene exposure ppm (mg/m^3)	No. of subjects, exposure time	Substance	Effects	Ref.
4 (17), GM max 103 (448) TA	233 (122 men, 111 women), occupational exposure	Xylene-toluene mixture	Subjective CNS symptoms; irritation of eyes, nose, throat	9
14 (60), GM 21 (90), AM max 175 (760) TA	175 (107 men, 68 women), occupational exposure, average 7 years	The three xylene isomers together made up >70% of the exposure	Subjective CNS symptoms, irritation of eyes, nose, throat	89
50 (218)	56 (28 men, 28 women) 2 hours	*m*-xylene	Increased subjective discomfort (CNS effects); irritation of eyes, nose, throat	23
70 (304)	16 men, 4 hours	*p*-xylene	No negative effect on psychological tests; no irritation of eyes, nose, throat	1
90 (392)	8 men, 6 days	*m*-xylene	CNS effects (reaction time, balance, coordination)	83
100 (434) TA	6 men, 6 hours/day for 2 weeks	*m*-xylene	CNS effects (reaction time)	82
100 (434)	10 men 4 hours	Not defined, probably pure xylene	CNS effects (reaction time)	15
110 (478)	6 volunteers 15 minutes	Mixture: 20% ethylbenzene	No eye irritation	7
200 (870)	10 volunteers 3 – 5 minutes	Not defined, probably pure xylene	More than half the subjects reported irritation of eyes, nose, throat	66
460 (2000)	15 minutes	Mixture: 20% ethylbenzene	Eye irritation	7

GM = Geometric mean
AM = Arithmetic mean
TA = Time-weighted averages

Table 2. Dose-effect relationships observed in animals experimentally exposed to xylenes.

Xylene exp. ppm (mg/m^3)	Species	Substance, exposure time	Effect	Ref.
100 (435)	Rat	*m*-xylene 6 hrs/day, 5 days/week, 4 weeks	Behavior changes in tests given 39 to 54 days after the exposure	32
160 (700)	Mongolian gerbil	18% *o*-, 70% *m*-, 12% *p*-xylene; <3% ethylbenzene, <0.1% toluene 4 months	Increase of glial cell markers and DNA in some parts of the brain	79
200 (870)	Rat	Industrial xylene (unspecified) 6 hrs/day, days 4-20 of gestation	Pups: delayed ossification; poorer results on learning and memory tests	34
450 (1960)	Rat	*p*-xylene 6 hrs/day, 6 days/week, 13 weeks	No damage to hearing	26
500 (2175)	Rat	*o*-xylene or industrial xylene (15% ethylbenzene, 21% *o*-, 44% *m*-, 19% *p*-xylene) 6 hrs/day, days 6-20 of gestation	Lower fetal weight on day 21 of gestation	81
500 (2175)	Rat	Industrial xylene (unspecified) 6 hrs/day, days 7-20 of gestation	Pups: Poorer performance on neuromotor, memory and learning tests, persisting to adulthood; more pronounced for females	35, 36
800 (3480)	Rat	10% *p*-, 80% *m*-, 10% *o*-xylene 6 weeks	Hearing damage	70
1360 (5900)	Mouse	*m*-xylene	RD_{50}	62
4300-6000 (18,700-26,100)	Rat, Mouse	All 3 isomers 6 hours	LC_{50}	42

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Summary

Montelius J (ed). *Scientific Basis for Swedish Occupational Standards*. XXVI. Arbete och Hälsa 2005:17:1-79. National Institute for Working Life, Stockholm.

Critical review and evaluation of those scientific data which are relevant as a background for discussion of Swedish occupational exposure limits. This volume consists of the consensus reports given by the Criteria Group at the Swedish National Institute for Working Life from July, 2004 through September, 2005.

Key Words: Aluminum trifluoride, Ammonium fluoride, Calcium fluoride, Hydrogen fluoride, Inorganic lead, Occupational exposure limit (OEL), Potassium fluoride, Risk assessment, Scientific basis, Sodium fluoride, Toxicology, Xylenes.

Sammanfattning

Montelius J (ed). *Vetenskapligt underlag för hygieniska gränsvärden*. XXVI. Arbete och Hälsa 2005:17:1-79. Arbetslivsinstitutet, Stockholm.

Sammanställningar baserade på kritisk genomgång och värdering av de vetenskapliga fakta, vilka är relevanta som underlag för fastställande av hygieniskt gränsvärde. Volymen omfattar de underlag som avgivits från Kriteriegruppen för hygieniska gränsvärden under perioden juli 2004 - September 2005.

Nyckelord: Aluminiumtrifluorid, Ammoniumfluorid, Fluorväte, Hygieniskt gränsvärde, Kalciumfluorid, Kaliumfluorid, Natriumfluorid, Oorganiskt bly, Riskvärdering, Toxikologi, Vetenskapligt underlag, Xylener.

En svensk version av dessa vetenskapliga underlag finns publicerad i Arbete och Hälsa 2005:16.

APPENDIX

Consensus reports in this and previous volumes

Substance	Consensus date	Volume in Arbete och Hälsa	(No.)
Acetaldehyde	February 17, 1987	1987:39	(VIII)
Acetamide	December 11, 1991	1992:47	(XIII)
Acetic acid	June15, 1988	1988:32	(IX)
Acetone	October 20, 1987	1988:32	(IX)
Acetonitrile	September 12, 1989	1991:8	(XI)
Acrylamide	April 17, 1991	1992:6	(XII)
Acrylates	December 9, 1984	1985:32	(VI)
Acrylonitrile	April 28, 1987	1987:39	(VIII)
Aliphatic amines	August 25, 1982	1983:36	(IV)
Aliphatic hydrocarbons, C_{10}-C_{15}	June 1, 1983	1983:36	(IV)
Aliphatic monoketons	September 5, 1990	1992:6	(XII)
Allyl alcohol	September 9, 1986	1987:39	(VIII)
Allylamine	August 25, 1982	1983:36	(IV)
Allyl chloride	June 6, 1989	1989:32	(X)
Aluminum	April 21, 1982	1982:24	(III)
revised	September 14, 1994	1995:19	(XVI)
Aluminum trifluoride	September 15, 2004	2005:17	(XXVI)
p-Aminoazobenzene	February 29, 1980	1981:21	(I)
Ammonia	April 28, 1987	1987:39	(VIII)
Ammonium fluoride	September 15, 2004	2005:17	(XXVI)
Amylacetate	March 23, 1983	1983:36	(IV)
revised	June 14, 2000	2000:22	(XXI)
Aniline	October 26, 1988	1989:32	(X)
Anthraquinone	November 26,1987	1988:32	(IX)
Antimony + compounds	December 8, 1999	2000:22	(XXI)
Arsenic, inorganic	December 9, 1980	1982:9	(II)
revised	February 15, 1984	1984:44	(V)
Arsine	October 20, 1987	1988:32	(IX)
Asbestos	October 21, 1981	1982:24	(III)
Barium	June 16, 1987	1987:39	(VIII)
revised	January 26, 1994	1994:30	(XV)
Benzene	March 4, 1981	1982:9	(II)
revised	February 24, 1988	1988:32	(IX)
Benzoyl peroxide	February 13, 1985	1985:32	(VI)
Beryllium	April 25, 1984	1984:44	(V)
Borax	October 6, 1982	1983:36	(IV)
Boric acid	October 6, 1982	1983:36	(IV)
Boron Nitride	January 27 1993	1993:37	(XIV)
Butadiene	October 23, 1985	1986:35	(VII)
1-Butanol	June 17, 1981	1982:24	(III)
Butanols	June 6, 1984	1984:44	(V)
Butyl acetate	June 6, 1984	1984:44	(V)
Butyl acetates	February 11, 1998	1998:25	(XIX)
Butylamine	August 25, 1982	1983:36	(IV)
Butyl glycol	October 6, 1982	1983:36	(IV)
γ-Butyrolactone	June 2 2004	2005:7	(XXV)

Cadmium	January 18,	1980	1981:21	(I)
revised	February 15,	1984	1984:44	(V)
revised	May 13,	1992	1992:47	(XIII)
revised	February 5	2003	2003:16	(XXIV)
Calcium fluorid	September 15,	2004	2005:17	(XXVI)
Calcium hydroxide	February 24,	1999	1999:26	(XX)
Calcium nitride	January 27,	1993	1993:37	(XIV)
Calcium oxide	February 24,	1999	1999:26	(XX)
Caprolactam	October 31,	1989	1991:8	(XI)
Carbon monoxide	December 9,	1981	1982:24	(III)
Cathecol	September 4,	1991	1992:47	(XIII)
Chlorine	December 9,	1980	1982:9	(II)
Chlorine dioxide	December 9,	1980	1982:9	(II)
Chlorobenzene	September 16	1992	1993:37	(XIV)
revised	April 2	2003	2003:16	(XXIV)
o-Chlorobenzylidene malononitrile	June 1,	1994	1994:30	(XV)
Chlorocresol	December 12,	1990	1992:6	(XII)
Chlorodifluoromethane	June 2,	1982	1982: 24	(III)
Chlorophenols	September 4,	1985	1986:35	(VII)
Chloroprene	April 16,	1986	1986:35	(VII)
Chromium	December 14,	1979	1981:21	(I)
revised	May 26,	1993	1993:37	(XIV)
revised	May 24,	2000	2000:22	(XXI)
Chromium trioxide	May 24,	2000	2000:22	(XXI)
Coal dust	September 9,	1986	1987:39	(VIII)
Cobalt	October 27,	1982	1983:36	(IV)
Cobalt and cobalt compounds	October 22	2003	2005:7	(XXV)
Copper	October 21,	1981	1982:24	(III)
Cotton dust	February14,	1986	1986:35	(VII)
Creosote	October 26,	1988	1989:32	(X)
Cresols	February 11,	1998	1998:25	(XIX)
Cumene	June 2,	1982	1982:24	(III)
Cyanamid	September 30,	1998	1999:26	(XX)
Cyanoacrylates	March 5,	1997	1997:25	(XVIII)
Cycloalkanes, C_5-C_{15}	April 25,	1984	1984:44	(V)
Cyclohexanone	March 10,	1982	1982:24	(III)
revised	February 24	1999	1999:26	(XX)
Cyclohexanone peroxide	February 13,	1985	1985:32	(VI)
Cyclohexylamine	February 7,	1990	1991:8	(XI)
Desflurane	May 27,	1998	1998:25	(XIX)
Diacetone alcohol	December 14,	1988	1989:32	(X)
Dichlorobenzenes	February 11,	1998	1998:25	(XIX)
1,2-Dibromo-3-chloropropane	May 30,	1979	1981:21	(I)
Dichlorodifluoromethane	June 2,	1982	1982:24	(III)
1,2-Dichloroethane	February 29,	1980	1981:21	(I)
Dichloromethane	February 29,	1980	1981:21	(I)
Dicumyl peroxide	February 13,	1985	1985:32	(VI)
Dicyclopentadiene	March 23,	1994	1994:30	(XV)
Diesel exhaust	December 4	2002	2003:16	(XXIV)
Diethanolamine	September 4,	1991	1992:47	(XIII)
Diethylamine	August 25,	1982	1983:36	(IV)
2-Diethylaminoethanol	January 25,	1995	1995:19	(XVI)
Diethylene glycol	September 16,	1992	1993:37	(XIV)
Diethyleneglycol ethylether + acetate	December 11,	1996	1997:25	(XVIII)
Diethyleneglycol methylether + acetate	March 13,	1996	1996:25	(XVII)
Diethyleneglycol monobutylether	January 25,	1995	1995:19	(XVI)
Diethylenetriamine	August 25,	1982	1983:36	(IV)

revised	January 25,	1995	1995:19	(XVI)
Diisocyanates	April 8,	1981	1982:9	(II)
revised	April 27,	1988	1988:32	(IX)
Diisopropylamine	February 7,	1990	1991:8	(XI)
N,N-Dimethylacetamide	March 23,	1994	1994:30	(XV)
Dimethyl adipate	December 9,	1998	1999:26	(XX)
Dimethylamine	December 10,	1997	1998:25	(XIX)
N,N-Dimethylaniline	December 12,	1989	1991:8	(XI)
Dimethyldisulfide	September 9,	1986	1987:39	(VIII)
Dimethylether	September 14,	1994	1995:19	(XVI)
Dimethylethylamine	June 12,	1991	1992:6	(XII)
Dimethylformamide	March 23,	1983	1983:36	(IV)
Dimethyl glutarate	December 9,	1998	1999:26	(XX)
Dimethylhydrazine	January 27,	1993	1993:37	(XIV)
Dimethyl succinate	December 9,	1998	1999:26	(XX)
Dimethylsulfide	September 9,	1986	1987:39	(VIII)
Dimethylsulfoxide, DMSO	December 11,	1991	1992:47	(XIII)
Dioxane	August 25,	1982	1983:36	(IV)
revised	March 4,	1992	1992:47	(XIII)
Diphenylamine	January 25,	1995	1995:19	(XVI)
4,4'-Diphenylmethanediisocyanate (MDI)	April 8,	1981	1982:9	(II)
reviderat	May 30	2001	2001:20	(XXII)
Dipropylene glycol	May 26,	1993	1993:37	(XIV)
Dipropyleneglycol monomethylether	December 12,	1990	1992:6	(XII)
Disulfiram	October 31,	1989	1991:8	(XI)
Enzymes, industrial	June 5,	1996	1996:25	(XVII)
Ethanol	May 30,	1990	1991:8	(XI)
Ethanolamine	September 4,	1991	1992:47	(XIII)
Ethylacetate	March 28,	1990	1991:8	(XI)
Ethylamine	August 25,	1982	1983:36	(IV)
Ethylamylketone	September 5,	1990	1992:6	(XII)
Ethylbenzene	December 16,	1986	1987:39	(VIII)
Ethylchloride	December 11,	1991	1992:47	(XIII)
Ethylene	December 11,	1996	1997:25	(XVIII)
Ethylene chloride	February 29,	1980	1981:21	(I)
Ethylene diamine	August 25,	1982	1983:36	(IV)
Ethylene glycol	October 21,	1981	1982:24	(III)
Ethylene glycol methylether + acetate	June 2,	1999	1999:26	(XX)
Ethyleneglycol monoisopropylether	November 16,	1994	1995:19	(XVI)
Ethyleneglycol monopropylether + acetate	September 15,	1993	1994:30	(XV)
Ethylene oxide	December 9,	1981	1982:24	(III)
Ethylenethiourea	September 27,	2000	2001:20	(XXII)
Ethylether	January 27,	1993	1993:37	(XIV)
Ethylglycol	October 6,	1982	1983:36	(IV)
Ferbam	September 12,	1989	1991:8	(XI)
Ferric dimethyldithiocarbamate	September 12,	1989	1991:8	(XI)
Flour dust	December 10,	1997	1998:25	(XIX)
Fluorides	September 15,	2004	2005:17	(XXVI)
Formaldehyde	June 30,	1979	1981:21	(I)
revised	August 25,	1982	1983:36	(IV)
Formamide	December 12,	1989	1991:8	(XI)
Formic acid	June 15,	1988	1988:32	(IX)
Furfural	April 25,	1984	1984:44	(V)
Furfuryl alcohol	February 13,	1985	1985:32	(VI)
Gallium + Gallium compounds	January 25,	1995	1995:19	(XVI)

Glutaraldehyde	September 30	1998	1999:26	(XX)
Glycol ethers	October 6,	1982	1983:36	(IV)
Glyoxal	September 13,	1996	1996:25	(XVII)
Grain dust	December 14,	1988	1989:32	(X)
Graphite	December 10,	1997	1998:25	(XIX)
Halothane	April 25,	1985	1985:32	(VI)
2-Heptanone	September 5,	1990	1992:6	(XII)
3-Heptanone	September 5,	1990	1992:6	(XII)
Hexachloroethane	September 15,	1993	1994:30	(XV)
Hexamethylenediisocyanate (HDI)	April 8,	1981	1982:9	(II)
revised	May 30,	2001	2001:20	(XXII)
Hexamethylenetetramine	August 25,	1982	1983:36	(IV)
n-Hexane	January 27,	1982	1982:24	(III)
2-Hexanone	September 5,	1990	1992:6	(XII)
Hexyleneglycol	November 17,	1993	1994:30	(XV)
Hydrazine	May 13,	1992	1992:47	(XIII)
Hydrogen bromide	February 11,	1998	1998:25	(XIX)
Hydrogen cyanide	February 7	2001	2001:20	(XXII)
Hydrogen fluoride	April 25,	1984	1984:44	(V)
revised	September 15,	2004	2005:17	(XXVI)
Hydrogen peroxide	April 4,	1989	1989:32	(X)
Hydrogen sulfide	May 4,	1983	1983:36	(IV)
Hydroquinone	October 21,	1989	1991:8	(XI)
Indium	March 23,	1994	1994:30	(XV)
Industrial enzymes	June 5,	1996	1996:25	(XVII)
Isocyanic Acid (ICA)	December 5	2001	2002:19	(XXIII)
Isophorone	February 20,	1991	1992:6	(XII)
Isopropanol	December 9,	1981	1982:24	(III)
Isopropylamine	February 7,	1990	1991:8	(XI)
Isopropylbenzene	June 2,	1982	1982:24	(III)
Lactates	March 29,	1995	1995:19	(XVI)
Lactate esters	June 2,	1999	1999:26	(XX)
Lead, inorganic	February 29,	1980	1981:21	(I)
revised	September 5,	1990	1992:6	(XII)
revised	December 8,	2004	2005:17	(XXVI)
Lithium and lithium compounds	June 4	2003	2003:16	(XXIV)
Lithium boron nitride	January 27,	1993	1993:37	(XIV)
Lithium nitride	January 27,	1993	1993:37	(XIV)
Maleic anhydride	September 12,	1989	1991:8	(XI)
Manganese	February 15,	1983	1983:36	(IV)
revised	April 17,	1991	1992:6	(XII)
revised	June 4,	1997	1997:25	(XVIII)
Man made mineral fibers	March 4,	1981	1982:9	(II)
revised	December 1,	1987	1988:32	(IX)
Mercury, inorganic	April 25,	1984	1984:44	(V)
Mesityl oxide	May 4,	1983	1983:36	(IV)
Metal stearates, some	September 15,	1993	1994:30	(XV)
Methacrylates	September 12,	1984	1985:32	(VI)
Methanol	April 25,	1985	1985:32	(VI)
Methyl acetate	March 28	1990	1991:8	(XI)
Methylamine	August 25,	1982	1983:36	(IV)
Methylamyl alcohol	March 17,	1993	1993:37	(XIV)
Methyl bromide	April 27,	1988	1988:32	(IX)
Methyl chloride	March 4,	1992	1992:47	(XIII)

Methyl chloroform	March 4,	1981	1982:9	(II)
4,4´-methylene-bis-(2-chloroaniline)	February 4	2004	2005:7	(XXV)
Methylene chloride	February 29,	1980	1981:21	(I)
4,4'-Methylene dianiline	June 16,	1987	1987:39	(VIII)
revised	October 3	2001	2002:19	(XXIII)
Methyl ethyl ketone	February 13,	1985	1985:32	(VI)
Methyl ethyl ketone peroxide	February 13,	1985	1985:32	(VI)
Methyl formate	December 12,	1989	1991:8	(XI)
Methyl glycol	October 6,	1982	1983:36	(IV)
Methyl iodide	June 30,	1979	1981:21	(I)
Methylisoamylamine	September 5,	1990	1992:6	(XII)
Methylisoamylketone	February 6	2002	2002:19	(XXIII)
Methylisocyanate (MIC)	December 5	2001	2002:19	(XXIII)
Methyl mercaptane	September 9,	1986	1987:39	(VIII)
Methyl methacrylate	March 17,	1993	1993:37	(XIV)
Methyl pyrrolidone	June 16,	1987	1987:39	(VIII)
α-Methylstyrene	November 1	2000	2001:20	(XXII)
Methyl-t-butyl ether	November 26,	1987	1988:32	(IX)
revised	September 30,	1998	1999:26	(XX)
Mixed solvents, neurotoxicity	April 25,	1985	1985:32	(VI)
MOCA	February 4	2004	2005:7	(XXV)
Molybdenum	October 27,	1982	1983:36	(IV)
Monochloroacetic acid	February 20,	1991	1992:6	(XII)
Monochlorobenzene	September 16,	1993	1993:37	(XIV)
Monomethylhydrazine	March 4,	1992	1992:47	(XIII)
Mononitrotoluene	February 20,	1991	1992:6	(XII)
Monoterpenes	February 17,	1987	1987:39	(VIII)
Morpholine	December 8,	1982	1983:36	(IV)
revised	June 5,	1996	1996:25	(XVII)
Naphthalene	May 27,	1998	1998:25	(XIX)
Natural crystallinic fibers (except asbestos)	June 12,	1991	1992:6	(XII)
Nickel	April 21,	1982	1982:24	(III)
Nicotine	June 2	2004	2005:7	(XXV)
Nitroethane	April 4,	1989	1989:32	(X)
Nitrogen oxides	December 11,	1985	1986:35	(VII)
Nitroglycerin	February 13,	1985	1985:32	(VI)
Nitroglycol	February 13,	1985	1985:32	(VI)
Nitromethane	January 6,	1989	1989:32	(X)
Nitropropane	October 28,	1986	1987:39	(VIII)
2-Nitropropane	March 29,	1995	1995:19	(XVI)
Nitroso compounds	December 12,	1990	1992:6	(XII)
Nitrosomorpholine	December 8,	1982	1983:36	(IV)
Nitrotoluene	February 20,	1991	1992:6	(XII)
Nitrous oxide	December 9,	1981	1982:24	(III)
Oil mist	April 8,	1981	1982:9	(II)
Organic acid anhydrides, some	September 12,	1989	1991:8	(XI)
Oxalic acid	February 24,	1988	1988:32	(IX)
Ozone	April 28,	1987	1987:39	(VIII)
Paper dust	February 7,	1990	1991:8	(XI)
Pentaerythritol	November 16,	1994	1995:19	(XVI)
1,1,1,2,2-Pentafluoroethane	February 24,	1999	1999:26	(XX)
Pentyl acetate	June 14,	2000	2000:22	(XXI)
Peroxides, organic	February 13,	1985	1985:32	(VI)
Phenol	February 13,	1985	1985:32	(VI)
Phosphorous chlorides	September 30,	1998	1999:26	(XX)

Phosphorous oxides	February 11, 1998	1998:25	(XIX)
Phthalates	December 8, 1982	1983:36	(IV)
Phthalic anhydride	September 12, 1989	1991:8	(XI)
Piperazine	September 12, 1984	1985:32	(VI)
Plastic dusts	December 16, 1986	1987:39	(VIII)
Platinum	June 4, 1997	1997:25	(XVIII)
Polyaromatic hydrocarbons	February 15, 1984	1984:44	(V)
Polyisocyanates	April 27, 1988	1988:32	(IX)
Potassium aluminium fluoride	June 4, 1997	1997:25	(XVIII)
Potassium cyanide	February 7 2001	2001:20	(XXII)
Potassium dichromate	May 24, 2000	2000:22	(XXI)
Potassium Fluoride	September 15, 2004	2005:17	(XXVI)
Potassium hydroxide	Marsh 15, 2000	2000:22	(XXI)
2-Propanol	December 9, 1981	1982:24	(III)
Propene	September 13, 1996	1996:25	(XVII)
Propionic acid	November 26, 1987	1988:32	(IX)
Propylacetate	September 14, 1994	1995:19	(XVI)
Propylene glycol	June 6, 1984	1984:44	(V)
Propylene glycol-1,2-dinitrate	May 4, 1983	1983:36	(IV)
Propylene glycol monomethylether	October 28, 1986	1987:39	(VIII)
Propylene oxide	June 11, 1986	1986:35	(VII)
Pyridine	May 13, 1992	1992:47	(XIII)
Quartz	March 13, 1996	1996:25	(XVII)
Resorcinol	September 4, 1991	1992:47	(XIII)
Selenium	December 11, 1985	1986:35	(VII)
revised	February 22, 1993	1993:37	(XIV)
Sevoflurane	May 27, 1998	1998:25	(XIX)
Silica	March 13, 1996	1996:25	(XVII)
Silver	October 28, 1986	1987:39	(VIII)
Sodium cyanide	February 7 2001	2001:20	(XXII)
Sodium Fluoride	September 15, 2004	2005:17	(XXVI)
Sodium hydroxide	August 24, 2000	2000:22	(XXI)
Stearates, metallic, some	September 15, 1993	1994:30	(XV)
Stearates, non-metallic, some	November 17, 1993	1994:30	(XV)
Strontium	January 26, 1994	1994:30	(XV)
Styrene	February 29, 1980	1981:21	(I)
revised	October 31, 1989	1991:8	(XI)
Sulfur dioxide	April 25, 1985	1985:32	(VI)
Sulfur fluorides	March 28, 1990	1991:8	(XI)
Synthetic inorganic fibers	March 4, 1981	1982:9	(II)
revised	December 1, 1987	1988:32	(IX)
revised	December 3, 2003	2005:7	(XXV)
Synthetic organic and inorganic fibers	May 30, 1990	1991:8	(XI)
Talc dust	June 12, 1991	1992:6	(XII)
Terpenes, mono-	February 17, 1987	1987:39	(VIII)
Tetrabromoethane	May 30, 1990	1991:8	(XI)
Tetrachloroethane	June 4, 1997	1997:25	(XVIII)
Tetrachloroethylene	February 29, 1980	1981:21	(I)
1,1,1,2-Tetrafluoroethane	March 29, 1995	1995:19	(XVI)
Tetrahydrofuran	October 31, 1989	1991:8	(XI)
Tetranitromethane	April 4, 1989	1989:32	(X)
Thioglycolic acid	June 1, 1994	1994:30	(XV)
Thiourea	December 1, 1987	1988:32	(IX)
revised	June 2, 1999	1999:26	(XX)

Thiram	October 31,	1989	1991:8	(XI)
Thiurams, some	October 31,	1989	1991:8	(XI)
Tin and inorganic tin compounds	October 22	2003	2005:7	(XXV)
Titanium dioxide	February 21,	1989	1989:32	(X)
Toluene	February 29,	1980	1981:21	(I)
revised	February 6	2002	2002:19	(XXIII)
Toluene-2,4-diamine	November 1,	2000	2001:20	(XXII)
Toluene-2,6-diamine	November 1,	2000	2001:20	(XXII)
Toluene-2,4-diisocyanate	April 8,	1981	1982:9	(II)
revised	May 30,	2001	2001:20	(XXII)
Toluene-2,6-diisocyanate	April 8,	1981	1982:9	(II)
revised	May 30,	2001	2001:20	(XXII)
1,1,1-Trifluoroethane	February 24,	1999	1999:26	(XX)
Trichlorobenzene	September 16,	1993	1993:37	(XIV)
1,1,1-Trichloroethane	March 4,	1981	1982:9	(II)
Trichloroethylene	December 14,	1979	1981:21	(I)
Trichlorofluoromethane	June 2,	1982	1982:24	(III)
1,1,2-Trichloro-1,2,2-trifluoroethane	June 2,	1982	1982:24	(III)
Triethanolamine	August 25,	1982	1983:36	(IV)
revised	October 23	2002	2003:16	(XXIV)
Triethylamine	December 5,	1984	1985:32	(VI)
Trimellitic anhydride	September 12,	1989	1991:8	(XI)
Trimethylolpropane	November 16,	1994	1995:19	(XVI)
Trinitrotoluene	April 17,	1991	1992:6	(XII)
Vanadium	March 15,	1983	1983:36	(IV)
Vinyl acetate	June 6,	1989	1989:32	(X)
Vinyl toluene	December 12,	1990	1992:6	(XII)
White spirit	December 16,	1986	1987:39	(VIII)
Wood dust	June 17,	1981	1982:9	(II)
revised	June 25,	2000	2000:22	(XXI)
Xylene	February 29,	1980	1981:21	(I)
revised	September 14,	2005	2005:17	(XXVI)
Zinc	April 21,	1982	1982:24	(III)
Zinc chromate	May 24,	2000	2000:22	(XXI)
Zinc dimethyl dithiocarbamate	September 12,	1989	1991:8	(XI)
Ziram	September 12,	1989	1991:8	(XI)

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